Therapeutic Interventional Trials in Traumatic Brain Injury

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COI

Inventor

DETECT™ Technology – a novel tool for detecting concussions

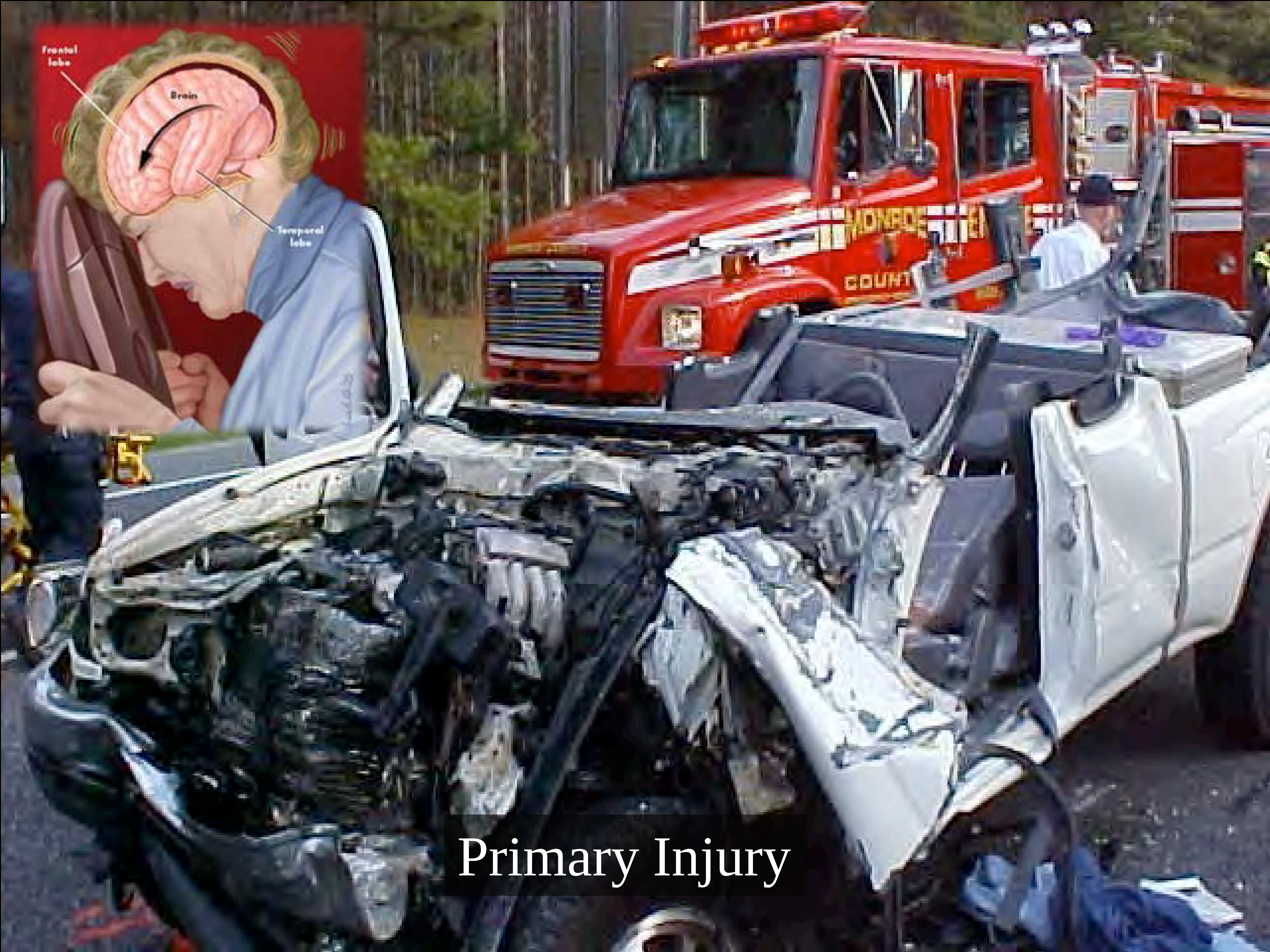
BHR Pharma – Inventor of technology licensed from Emory to create path for progesterone technology to consumer. Eligible for Royalties through Emory University.

EMORY

Public Health Burden of TBI in the United States

Faul, M et al. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010

175 Airliners

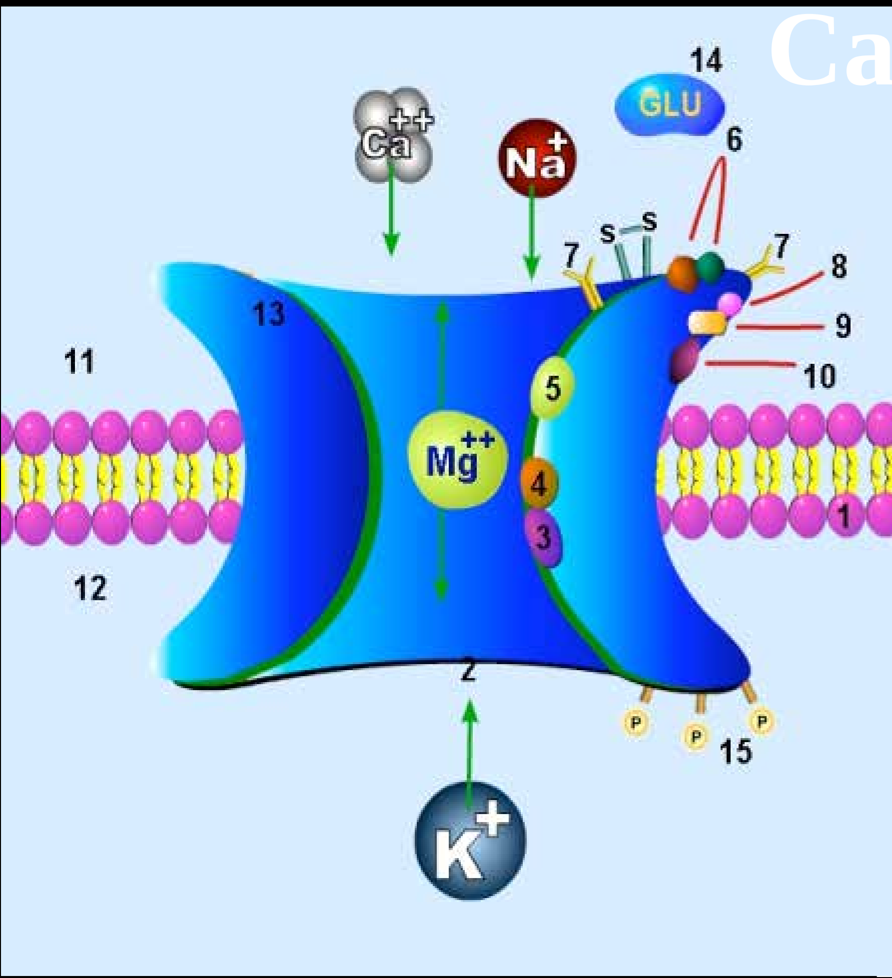


Primary Injury

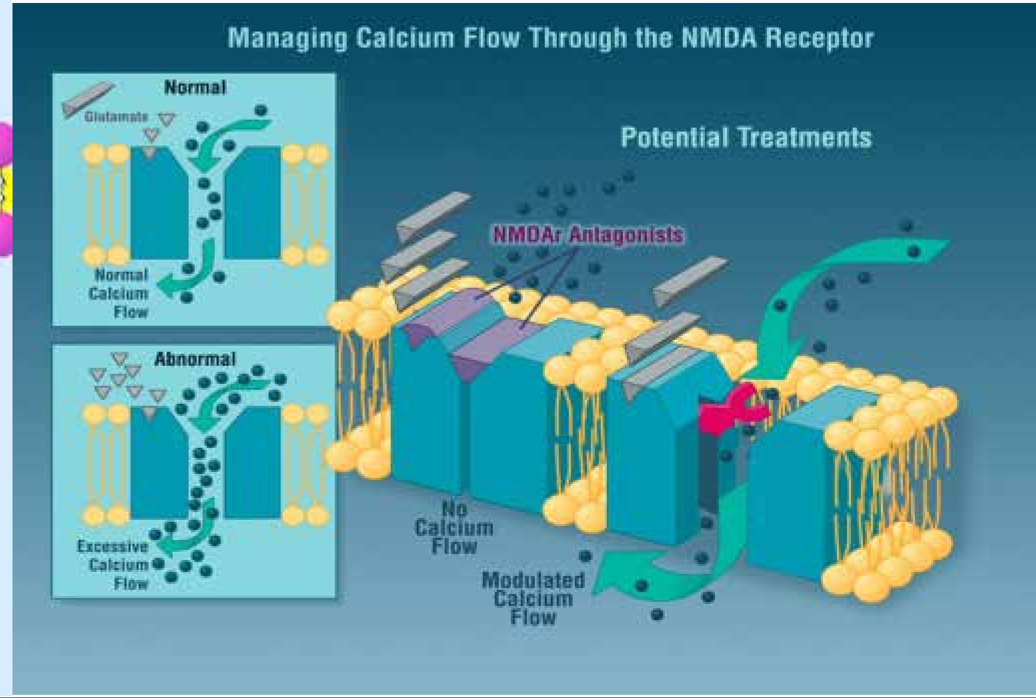
Secondary Injury

Neurotoxic

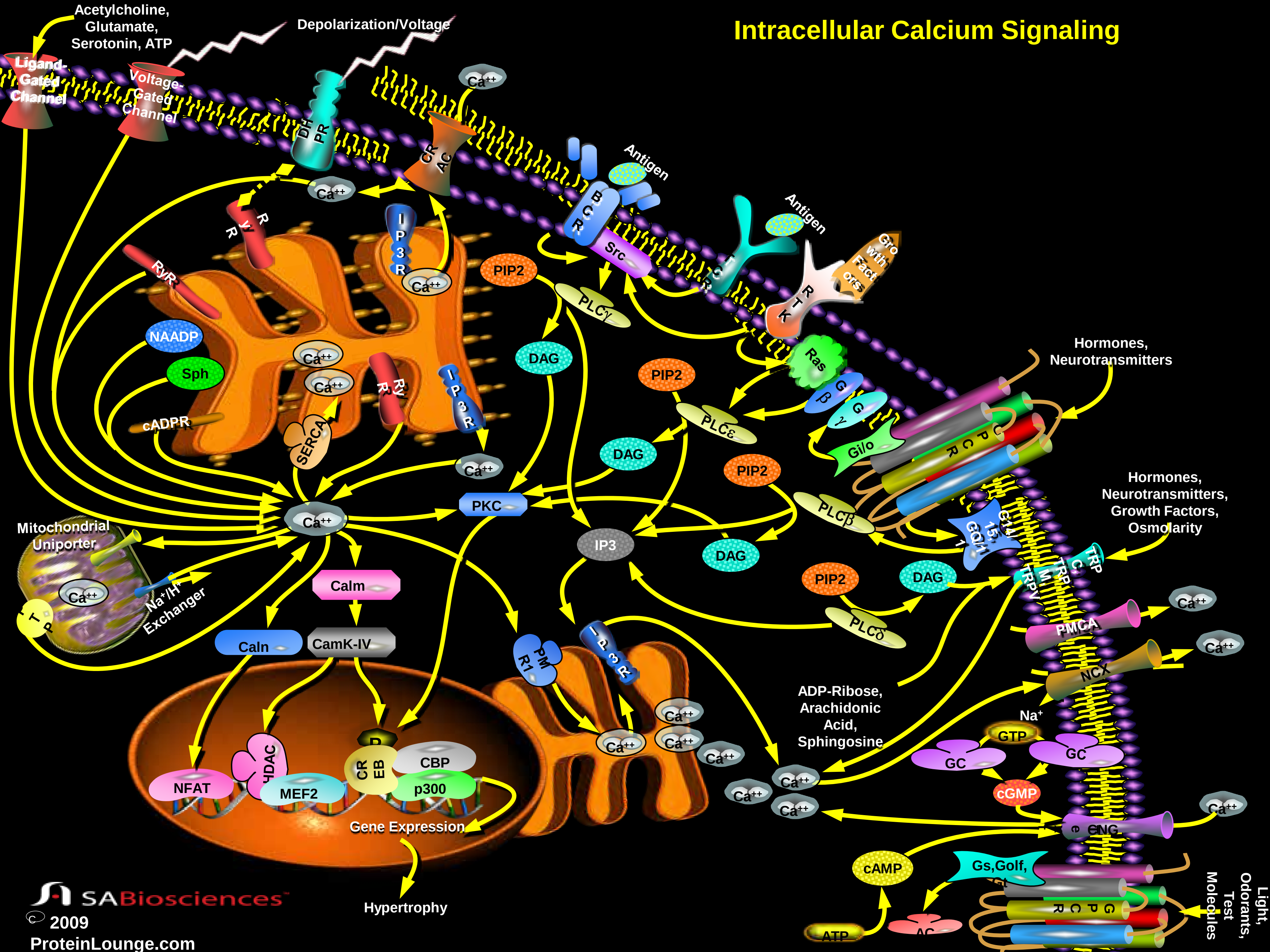
Ca



- **Excitatory Amino Acids**
  - Glutamate, Glycine, others
- **Critical Ions**
  - Calcium, Sodium, Magnesium



- **Receptor Activation**
  - NMDA, AMPA, etc.


Intracellular Calcium Signaling
Acetylcholine, Glutamate, Serotonin, ATP
Depolarization/Voltage
Ligand-Gated Channel
Voltage-Gated Channel
DHPR
CRAC
Ca++
Antigen
BCR
Src
TCR
RTK
Growth Factors
RyR
IP3R
NAADP
Sph
cADPR
SERCA
PIP2
PLCγ
DAG
PLCε
Ras
Gβ
Gγ
Gi/o
GPCR
Hormones, Neurotransmitters
PKC
IP3
PLCβ
G14, 15, Gq/11
Hormones, Neurotransmitters, Growth Factors, Osmolarity
TRPC
TRPM
TRPV
PLCδ
PMCA
NCX
Mitochondrial Uniporter
Na+/H+ Exchanger
Calm
CamK-IV
Caln
PMR1
ADP-Ribose, Arachidonic Acid, Sphingosine
Na+
GTP
GC
cGMP
CNG
NFAT
HDAC
MEF2
CREB
CBP
p300
P
Gene Expression
Hypertrophy
cAMP
Gs,Golf,
ATP
AC
Light, Odorants, Test Molecules
SABiosciences
2009
ProteinLounge.com

Secondary Cascade after TBI

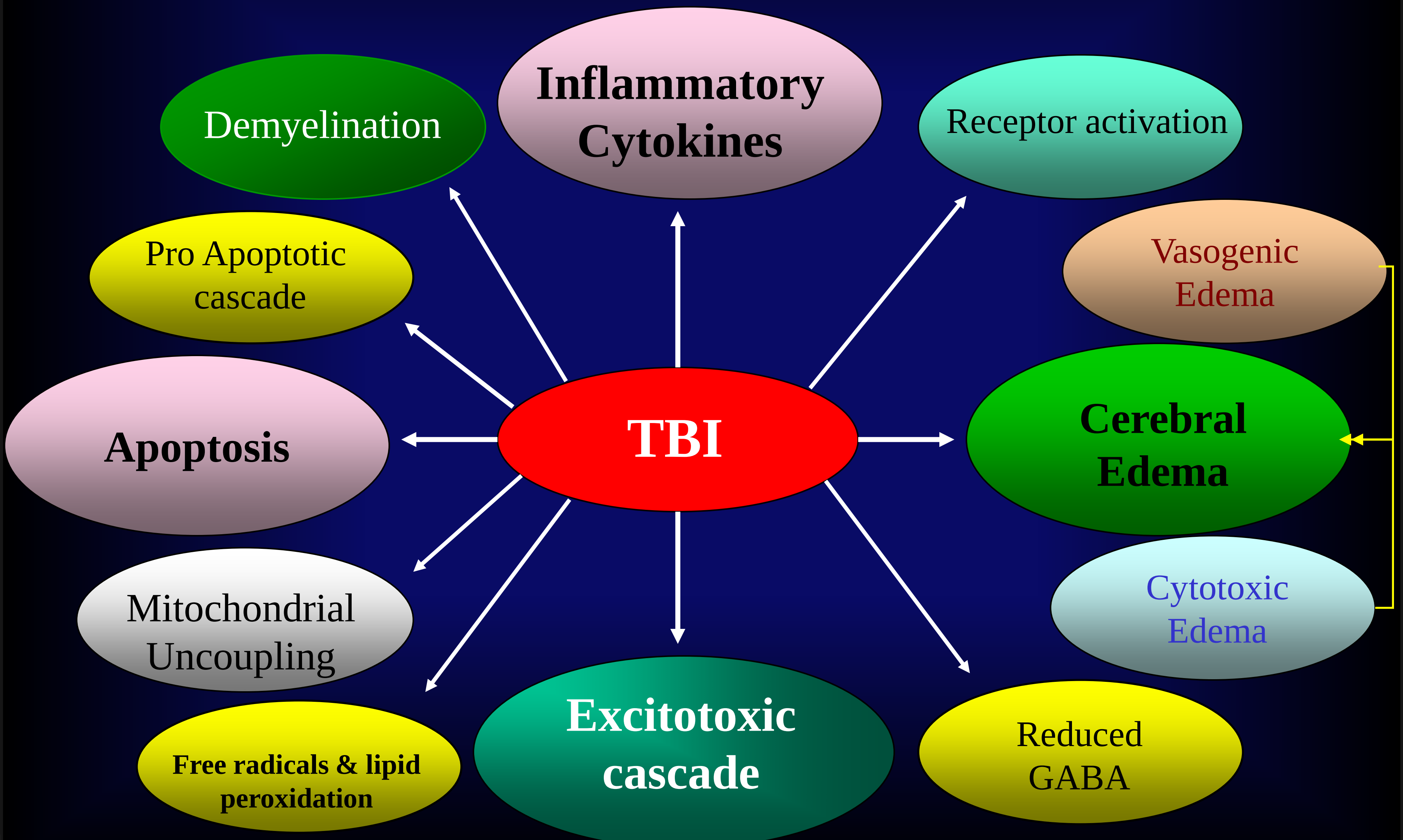


TABLE 4. Neuroprotection by *N*-Methyl-D-aspartate Receptor Modulation in Animal Models of Traumatic Brain Injury[a]

Mechanism of Action	Agent	Model	Series (Ref. No.)	Outcome
Ion channel blockade	Phencyclidine	FP	Hayes et al. (28)	Improved motor outcome
	MK-801	FP	McIntosh et al. (46)	Improved motor outcome
	MK-801	FP	McIntosh et al. (47)	Decreased edema, maintained ion homeostasis and $[Mg^{2+}]_i$, improved bioenergetic status
	MK-801	WD	Shapira et al. (61)	Improved motor outcome, decreased edema
	MK-801	FP	Hamm et al. (26)	Improved cognitive outcome
	MK-801	SDH	Kuroda et al. (36)	Decreased infarction volume
	MK-801	FP + ECX	Phillips et al. (55)	Improved cognitive outcome
	MK-801	CC	Nordqvist et al. (53)	Blocked expression of IGF-1
	Ketamine	FP	Smith et al. (65)	Improved cognitive outcome
	Ketamine	WD	Shapira et al. (60)	Maintained cation homeostasis
	Dextromethorphan	FP	Golding and Vink (22)	Maintained $[Mg^{2+}]_i$, improved bioenergetic status
	Dextrorphan	FP	Faden et al. (19)	Improved motor outcome, maintained $[Mg^{2+}]_i$, improved bioenergetic status
	Dextrorphan	FP	Panter and Faden (54)	Decreased glutamate release
Competitive antagonist	CPP	FP	Faden et al. (19)	Improved motor outcome
	CGS19755	FP	Panter and Faden (54)	Decreased glutamate release
	CGS19755	SDH	Kuroda et al. (36)	Decreased infarction volume
	APV	FP	Kawamata et al. (34)	Decreased hypermetabolism
	D-CPP-ene	SDH	Inglis et al. (30)	Decreased glucose hypermetabolism
	D-CPP-ene	SDH	Kuroda et al. (36)	Decreased infarction volume
	HU-211	WD	Shohami et al. (64)	Improved motor outcome, decreased BBB breakdown
	HU-211	WD	Shohami et al. (63)	Improved cognitive outcome
	HU-211	WD	Nadler et al. (51)	Decreased Ca^{2+} accumulation
	CP101,606	SDH	Tsuchida et al. (70)	Decreased infarction volume

[a] FP, fluid percussion; CC, cortical contusion; ECX, entorhinal cortex lesion; SDH, subdural hematoma; WD, weight drop; IGF-1, insulin-like growth factor-1; BBB, blood-brain barrier; $[Mg^{2+}]_i$, intracellular Mg^{2+} concentration; CPP, cerebral perfusion pressure; APV, aminophosphovalerate; CPP-ene, D-3-(2-carboxypiperazin-4-yl)propenyl-1-phosphonic acid (EAA494).

TABLE 1. Completed "Neuroprotection" Clinical Trials in Severe Traumatic Brain Injury, February 1999[a]

Series (Ref. No.)	Agent	No. of Patients/Country	Outcome/Comments
Ward (74)	Atropine	20, USA	Uncontrolled, "clinical improvement"
Heppner and Diemath (29)	Biperiden (anticholinergic)	200, Germany	Uncontrolled, shorter hospitalization, reduced duration of coma
Grumme et al. (25)	Corticosteroids	396, Germany	Only post hoc subgroup analysis positive
Schwartz et al. (59)	Mannitol versus pentobarbital	59, Canada	Randomized crossover permitted, mannitol group had better outcomes
Ward et al. (75)	Barbiturates (prophylaxis)	53, USA	DBPCRT, no benefit
Eisenberg et al. (17)	Barbiturates (therapeutic)	73, USA	DBPCRT, benefit to subset with uncontrolled ICP
Wolf et al. (77)	THAM (tromethamine buffer)	149, USA	DBPCRT, reduced deleterious effects of hyperventilation
Teasdale et al. (67)	Nimodipine (HIT I) (Ca^{2+} channel antagonist)	255, UK and Finland	DBPCRT, no benefit
European Study Group (18)	Nimodipine (HIT II)	840, EU	DBPCRT, improved outcomes in subset of SAH patients
Muizelaar et al. (50)	PEG-SOD (free radical scavenger) (Phase II)	94, USA	DBPCRT, ICP lower, outcome better ($P < 0.01$)
Young et al. (82)	PEG-SOD (Phase III), three dose levels	463, USA	DBPCRT, trend for 9% better outcomes ($P = 0.15$)
Bullock et al. (10)	CGS19755 (NMDA receptor antagonist)	113, USA and UK	DBPCRT, ICP lower
Alves and Jane	Tirilazad (aminosteroid antioxidant)	1170, USA and Canada	DBPCRT, no benefit (report awaited)
Marshall and Marshall (43, 44)	Tirilazad	1128, EU and Australia	DBPCRT, no benefit (report awaited)
Bullock and Marshall	Selfotel (CGS19755)	266, USA and Israel; 426, EU and Australia	DBPCRT, both terminated because of high mortality rates in concomitant stroke trials–no benefit (report awaited)
Cohadon	Synthelabo Eliprodil (SL 82) (Phase II)	453, France	DBPCRT, better outcome in "brain swelling" patients (report awaited)
Harders et al. (27)	Nimodipine (Phase II)	123, Germany (only SAH patients selected)	DBPCRT, 55% relative reduction in bad outcome at 6 mo ($P < 0.002$)
Gamzu	Cerestat (CNS 1102) (noncompetitive NMDA receptor antagonist)	512, USA and EU	DBPCRT, terminated because of high mortality rates in concomitant stroke trial, no benefit (report awaited)
Nichols	Bradycor (bradykinin receptor antagonist)	133, USA	DBPCRT, 10% trend toward better outcome (report awaited)
National Institutes of Health	Moderate hypothermia (32–33°C)	~500, USA	DBPCRT, data in analysis
Parke-Davis	SNX-111	~600, USA and EU	DBPCRT, prematurely halted, data in analysis
Sandoz/Novartis	SDZ EAA 494	~400, EU	DBPCRT, data in analysis
Pharmos	HU-211, dexanabinol	Israel	DBPCRT, data in analysis

[a] USA, United States of America; EU, European Union; UK, United Kingdom; DBPCRT, double-blind, placebo-controlled, randomized trial; HIT, Head Injury Trial; ICP, intracranial pressure; SAH, subarachnoid hemorrhage; PEG-SOD, polyethylene glycol-conjugated superoxide dismutase; NMDA, *N*-methyl-D-aspartate; THAM, tromethamine.

Completed "Neuroprotection" Clinical Trials in Severe Traumatic Brain Injury, February 1999 [a]

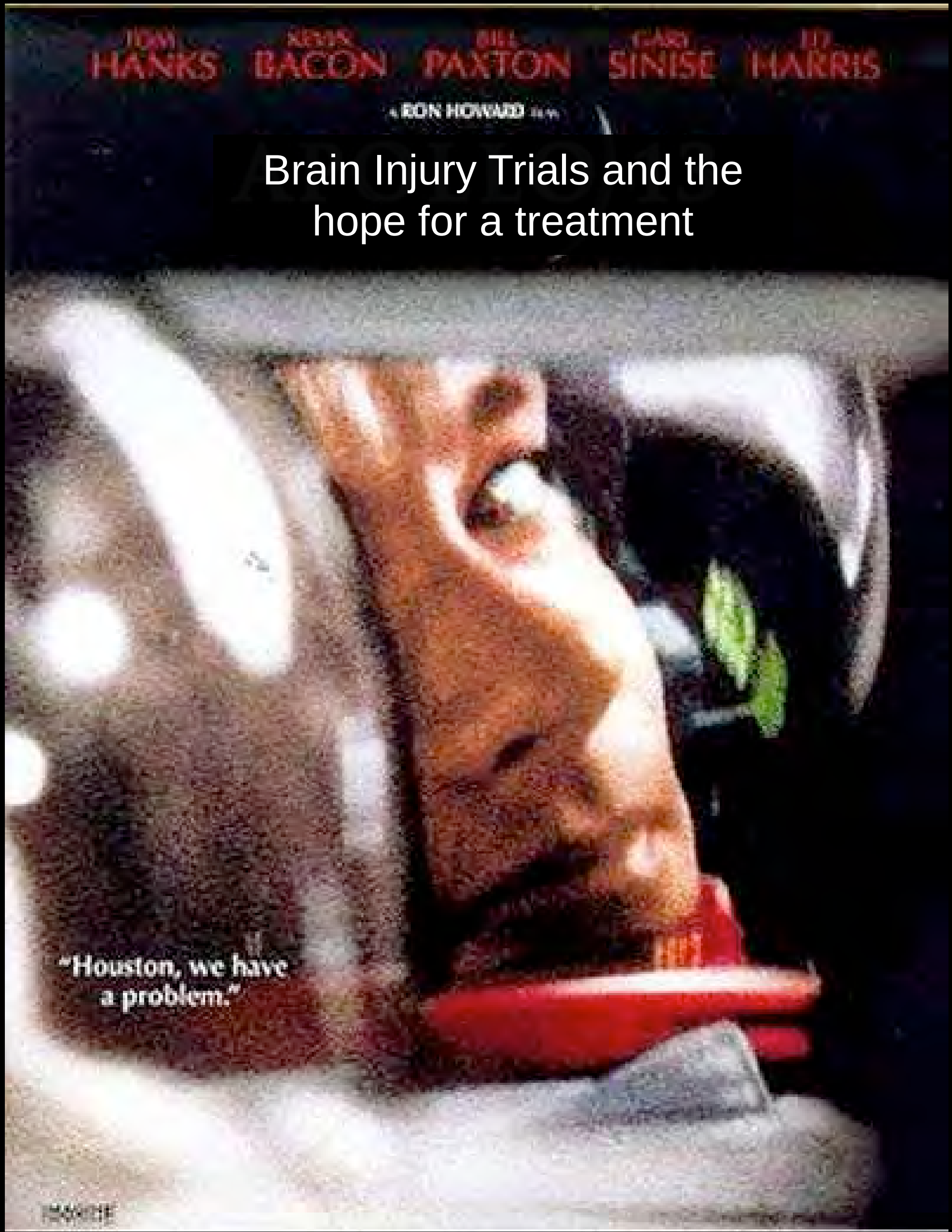
USA, United States of America; EU, European Union; UK, United Kingdom; DBPCRT, double-blind, placebo-controlled, randomized trial; HIT, Head Injury Trial; ICP, intracranial pressure; SAH, subarachnoid hemorrhage; PEG-SOD, polyethylene glycol-conjugated superoxide dismutase; NMDA, N-methyl-D-aspartate; THAM, tromethamine.

Failure of past TBI clinical Trials

- "None of the available medical therapies provide substantial relief from oedema and raised ICP, or at best, they are temporizing in most cases." *Ayata C and Ropper, A, J Clin Neurosci 9, 2002.*
- Hypothermia trials have been inconclusive (Interagency meeting on TBI, Washington, DC 2006).
- 50 compounds in 30 TBI trials over 30 years—all failed. Most recently:
- Methylprednisolone (CRASH trial) Failed
- Magnesium Sulfate   Failed
- Dexanabinol   Failed
- Tirilizad   Failed

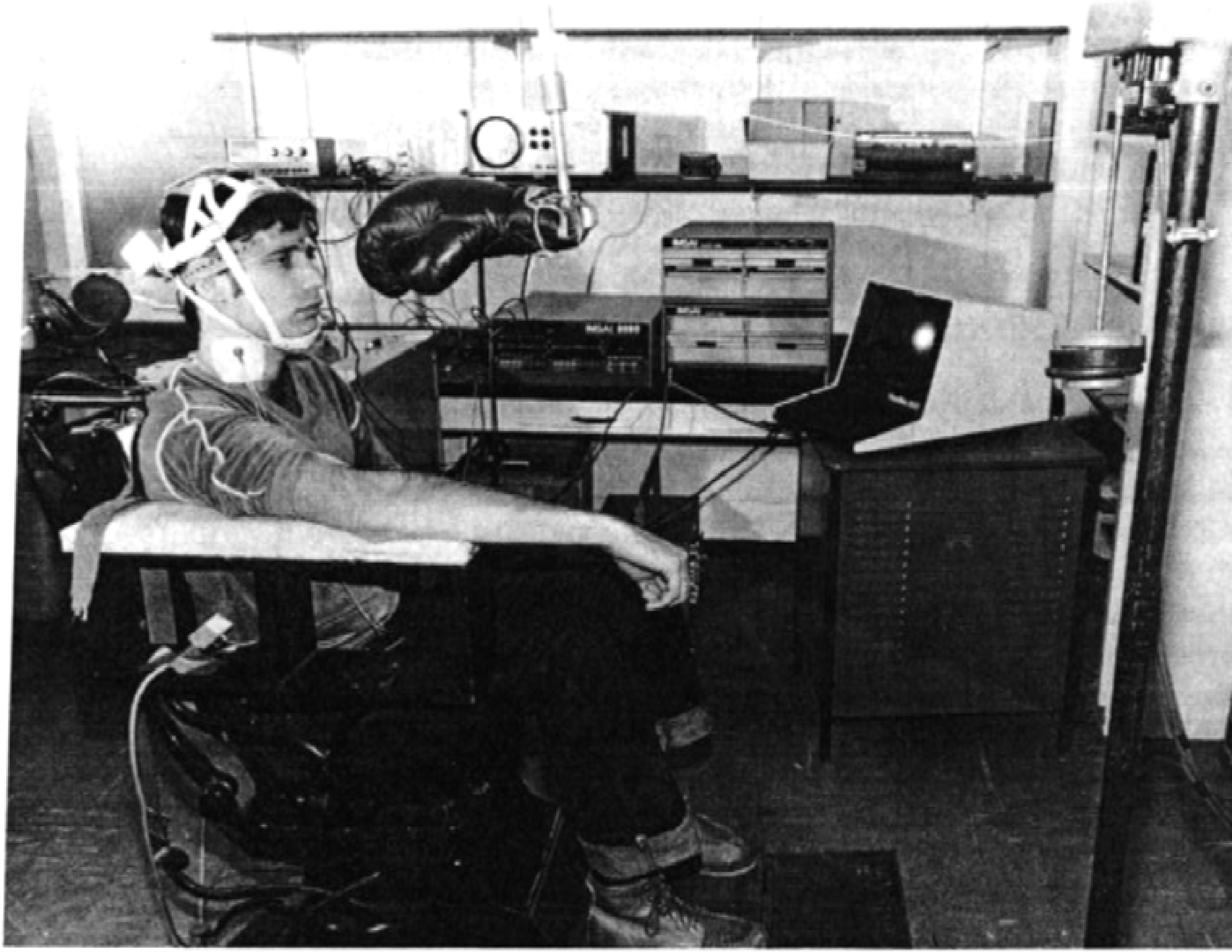
At Present There Are No Effective Drug Treatments For Traumatic Brain Injury

Brain Injury Trials and the hope for a treatment



HUGE GAPS in RESEARH still EXIST!

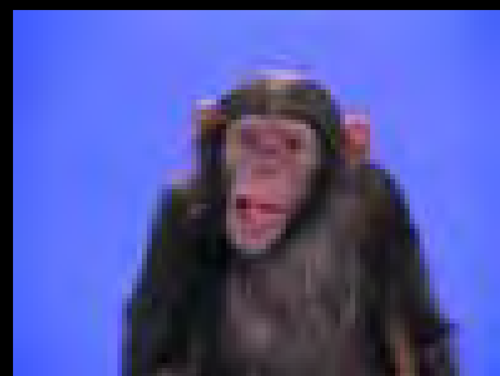
Benchtop to Bedside – are our models correct?



ProTECT

Is the Animal model relevant?

? =



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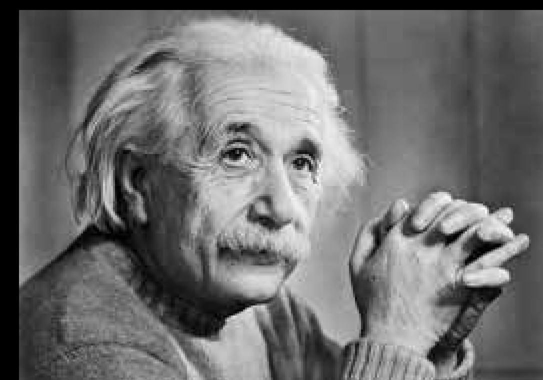
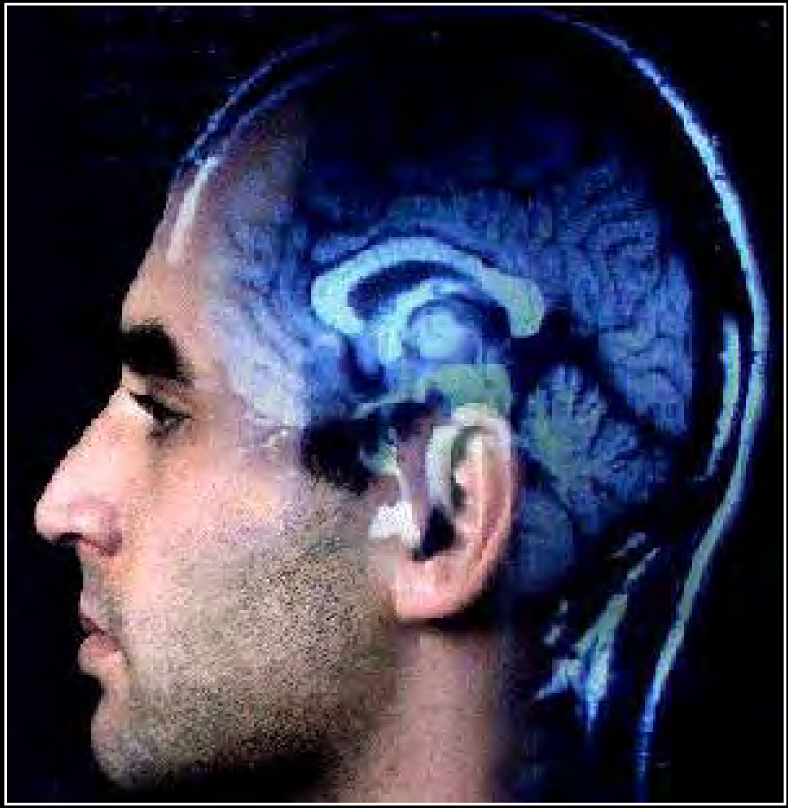


90%

98.5%

TBI classification

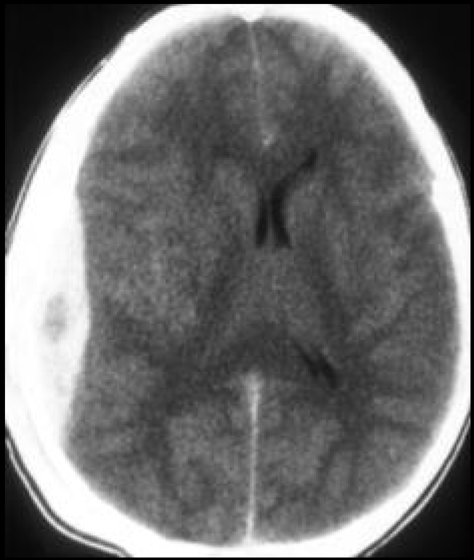
- Mild (GCS 14-15)
- Moderate (GCS 9-13)
- Severe (GCS 3-8)



Glasgow Coma Score

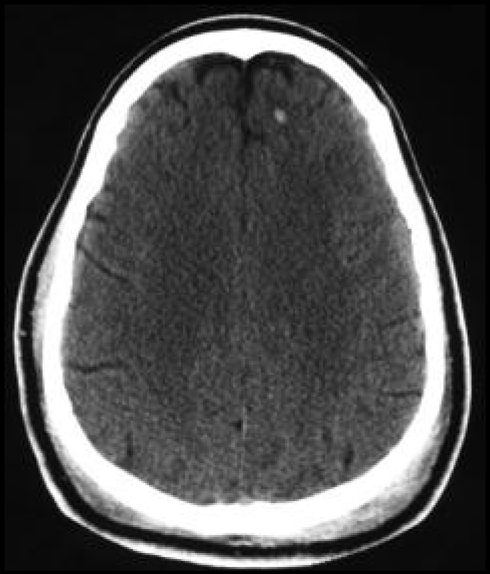
Finding	Pediatric Specific	Score
E — **EYE OPENING**		
Spontaneously		4
To speech		3
To pain		2
No response		1
V — **VERBAL RESPONSE**		
Alert & oriented	Smiles/Coos	5
Converses but disoriented	Inappropriate cries	4
Speaking nonsensical	Persistent scream	3
Moans, unintelligible sounds	Grunts	2
No response		1
M — **MOTOR**		
Follows commands	Spontaneous move	6
Localizes to pain		5
Movement or withdrawal to pain		4
Abnormal flexion (decorticate)		3
Abnormal extension (decerebrate)		2
No response		1
		15

6 Different Examples of Severe TBI



Epidural hematoma

Contusion/Hematoma

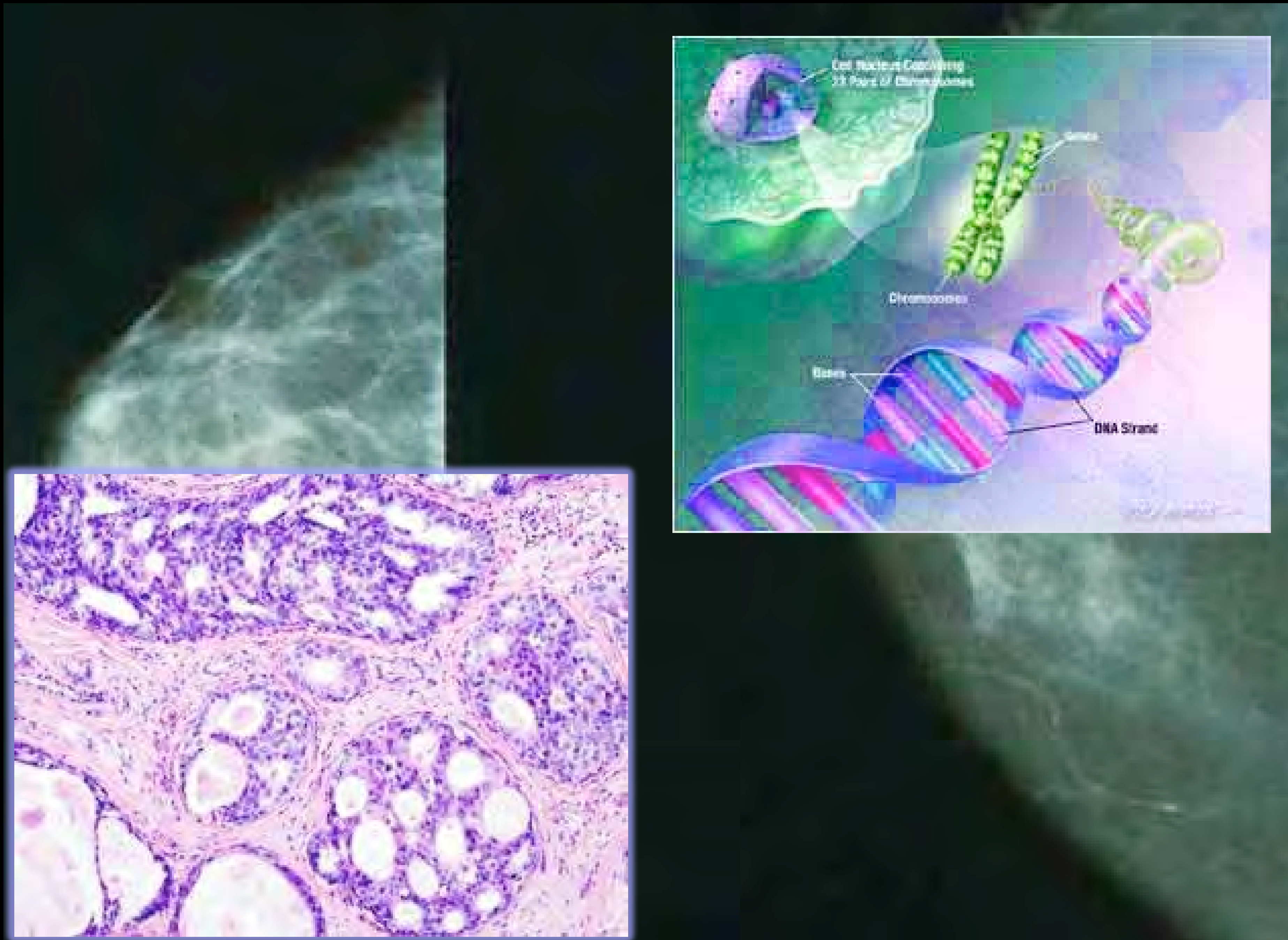


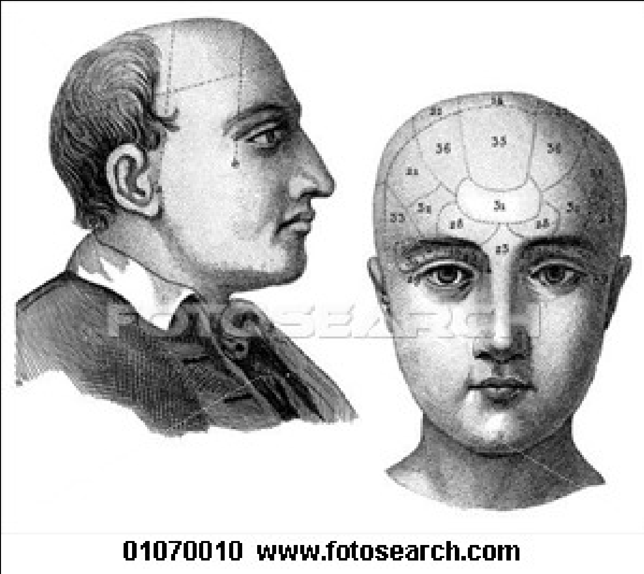
Diffuse axonal injury

Subdural hematoma

Subarachnoid hemorrhage

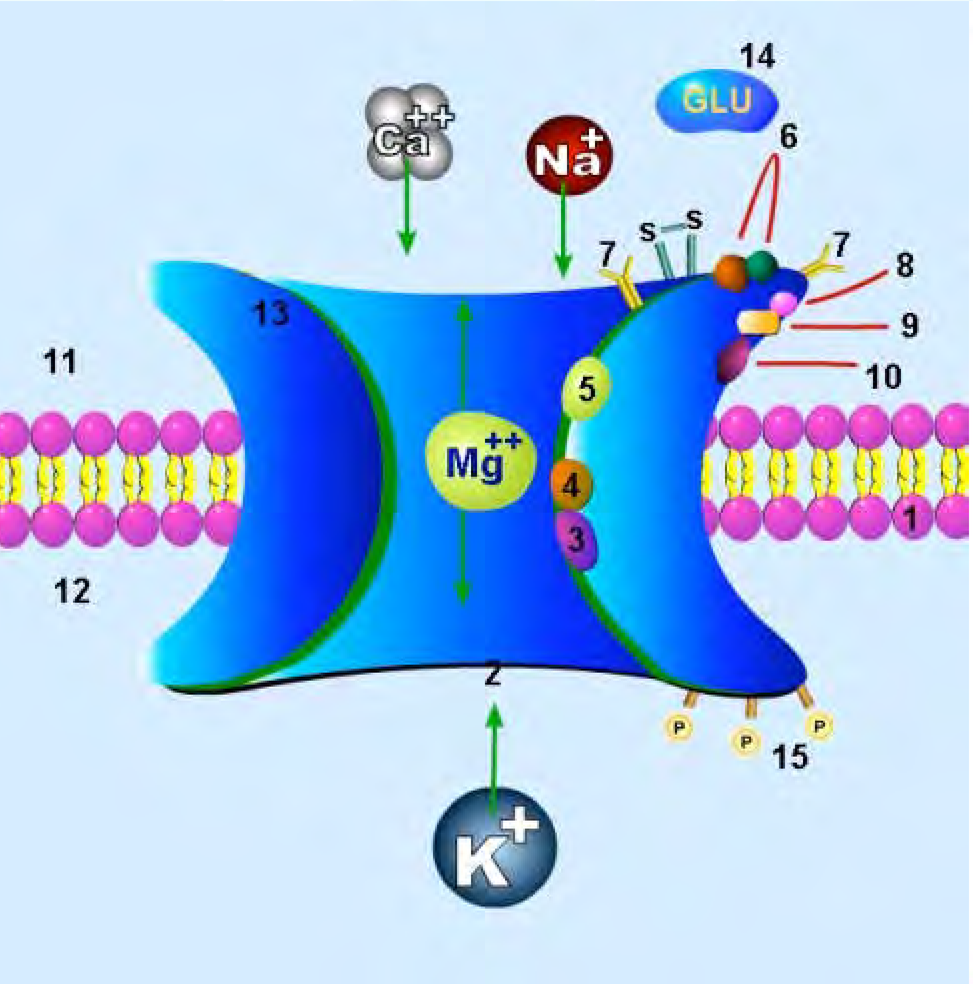
Diffuse swelling


Bases
DNA Strand


01070010 www.fotosearch.com


Bettmann/CORBIS

Is our approach wrong?



- Mechanistic Approach
- Single Target

"The magic bullet"

Potential mechanisms in TBI

Remyelina

Increases Bcl2
AkT-P

Reduce Apoptosis

Mitochondrial
Recoupling

**Decreases free
radicals & lipi
peroxidation**

gonizes
Receptor

Vasogenic
Edema

**luces Cerebral
Edema**

Cytotoxic
Edema

ances
ABA

Lack of evidence for current approach = treatment variability

Death "Knell"

☐ Pulse Ox ≥ 90%	☐ ICP < 20 mmHg	☐ Physiologic Na+ 135-145*
☐ PaO2 ≥ 100 mmHg	☐ PbtO2 ≥ 15 mmHg	☐ INR ≤ 1.4
☐ PaCO2 35-45 mmHg	☐ **CPP ≥ 60 mmHg**	☐ PLTS ≥ 75 x 10^3 / mm^3
☐ SBP ≥ 100 mmHg	☐ Temp 36.0-38.1°C	☐ Hgb ≥ 8 gm/dl
☐ pH 7.35-7.45	☐ Glucose 80-180 mg/dL	

**Hypertonic saline therapy: Na+ range: 145 mmol/L (minimum) to 160 mmol/L (maximum)*

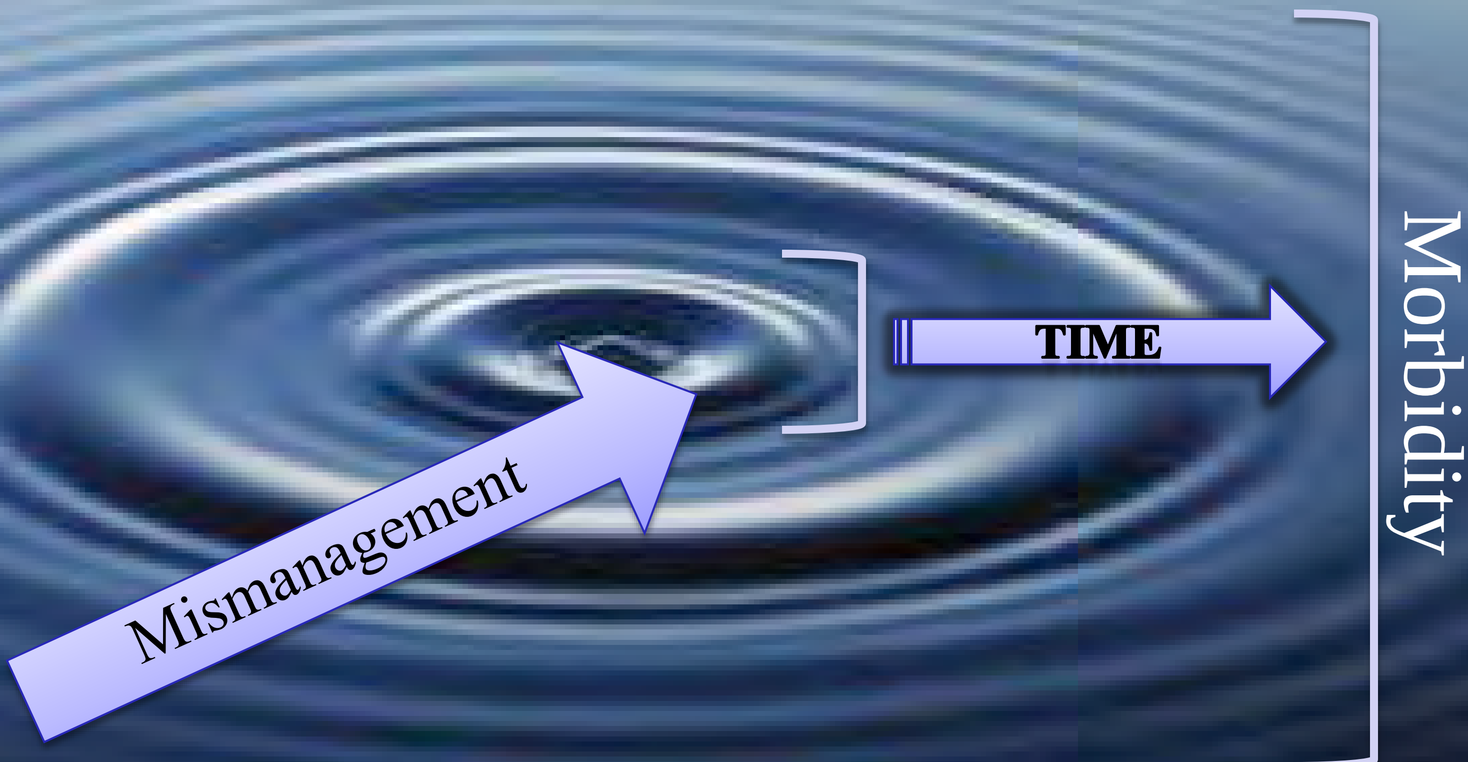
Published Mortality Rate for Severe TBI

1. Stein, SC., J of Neurotrauma 2010 (Meta-Analysis)	35%
2. Ottochian M, Am J Surgery, 2009	38%
3. O'Phelan K., Journal of Trauma, 2008	51%
4. Stiefel M.F., Journal of Neurosurgery, 2005 (with PO2 monitoring)	25%
5. Lu J., Acta Neurochirurgica, 2005	27%
6. Fakhry, S.M., J. Trauma 2004, 56:492-500	18%
7. Cooper, D.J., JAMA 2004, 291:1350-1357	45%
8. Gan, B.K., Ann Acad Med Singapore 2004, 33:63-67	45%
9. MRC Crash Trial, Curr Opin Crit Care 2003, 9:92-97	39%
10. Palmer S., Journal of Trauma, 2001	16%
11. Stein, SC., J of Neurotrauma 2010 (Meta-Analysis)	35%

Wide range of mortality reported in the literature – treatment variability

…a single episode of hypoxia & hypotension increased the mortality by 150%…

Chestnut et. al.. 1991



Time and timing have never matter so much

PHASE I-II Studies Acute Interventional

Drug	Site/Sponsor	Recruit	Subjects	Type	Outcome / Year completion
Esmolol/Propranolol (CHAIN)	JHU	N	34	Open	HR, Hyperadrenergic Activity (2015)
ABELADRUG200 (AbelaTBI2)	OSU, UC-Irvine Abela Pharma	Y	30	Open	ICP, Mortality, GOSE Severe TBI (2011)
Hypernatremia (MGH-HH5)	MGH	N	40	Open	Prevention of cerebral edema (2013)
BM Mononuclear Cells	UT-Houston DOD	Y	20	Open	Safety, NeuroEvents, GOSE, DRS (2014)
Probenecid & N-Acetyl Cysteine (ProNAC)	U-PITT NIH-NINDS	Y	20	DB	AE, Anti oxidant Reserve - Pediatric
Minocycline	Wayne State U	Y	14	Open	DRS, drug levels, CVLT, SF12 (2013)

Clinicaltrials.gov – Traumatic Brain Injury-Open Studies-Interventional-Phase II-III

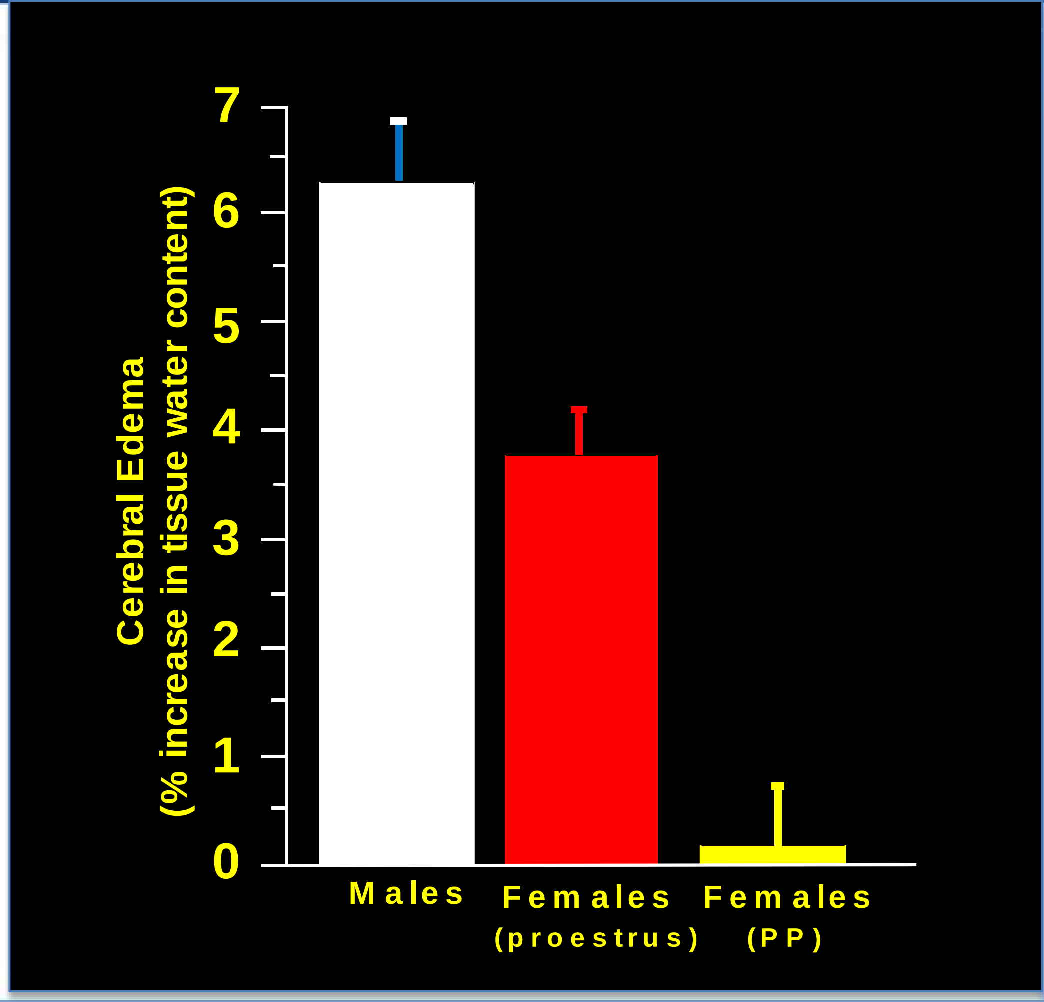
PHASE II Studies Acute Interventional

Drug	Site/Sponsor	Recruit	Subjects	Type	Outcome / Year completion
Propranolol (EPAT)	Cedars-Sinai	Y	40	Open	Safety Sympathetic storm (2015)
Lactate (LS_TCC)	Unv. Vaudois Swiss NSF, ESICM	Y	30	Open	Safety BT02, cellular Lactate Pyruvate (2015)
Propranolol/Clonidine (DASH)	Vanderbilt	Y	100	DB	Vent free days, Catechol levels, LOS, GOSE, NP,QOL (2016)
Atorvastatin	Baylor, UT-H Mission Connect DOD	Y	200	DB	mTBI, less PTS, PTSD, Cog recovery, safety, (2013)
HBO (HBO2T)	VCU, HHM VA US Navy NOMI	Y	60	DB	mTBI - Safety, NP, eye track, etc. (2011)
Brain Tiss Mon (BOOST II)	PITT, UT-SW, mutli NINDS-NIH	Y	182	SB	SevTBI Reduction of time BTO below 20 RR for GOS (2014)
Mild HypoTherm & Mg MHS-TBI	(DOD)	Y	105	Open	GOS, Vasospasm (2012)
NGF IN (NGF-TBI)	Jinling, China	N	118	DB	GOS, Neurologic Functions HAMA (2012)
Allopregnanolone	UC Davis DOD	N	136	DB	GOSE, Mort, NP, QOL, Sz, Safety (2015)
D-Cycloserine (DCS)	Hadassah	N	100	DB	ModTBI – NP test, GOSE (2014)
Paracetamol (PARITY)	Sidney, Wales The George Instit	Y	80	DB	Core Body temp, BP, cerebral hypoperfuse (2013)
Glyburide (RPI202)	U-Maryland, InTRuST AMRMC - DOD	Y	100	DB	Edema/Hemorrhage change, Mort, AE
hCG and Epoetin (NTx-265)	U-Calgary Stem Cell Therapeutics	Y	10	Open	Tier 1 Safety (2012)
Sevoflurane (SEPIA)	Assistance Publique Paris MOH, France	Y	27	Open	ICP, sedation, hemodynamics (2013)
NNZ-2566 (INTREPID2566)	U-Miami multi Neuren Pharmaceuticals	Y	260	DB	Safety, GOSE, NP, PK Biomarkers, EEG

PHASE III Studies Acute Interventional

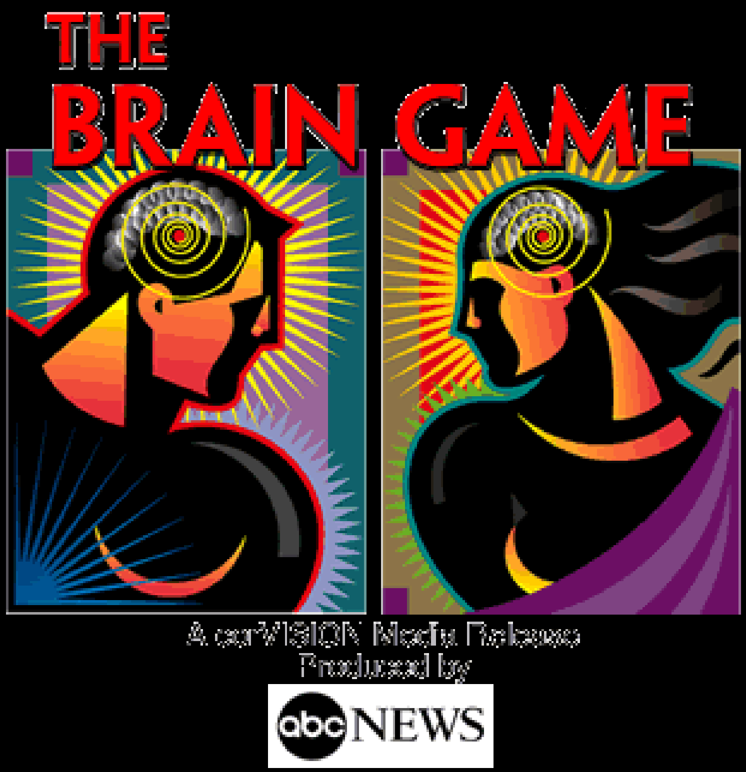
Drug	Site/Sponsor	Recruit	Subjects	Type	Outcome / Year completion
Erythropoietin (EPO-TBI)	Aus, NZ, NHMRC -Aus	Y	606	DB	GOSE dichot, NO, other, Safety (2014)
Proph Hypotherm (POLAR-RCT)	Aus, NZ, NHMRC -Aus	Y	512	SB	SevTBI Same Biomarkers (2013)
Progesterone (ProTECT III)	Emory, NETT NINDS-NIH	Y	1140	DB	GOSE, DRS, M, NP. (2015)
Progesterone (SyNAPSe)	Multi BHR	Y	1180	DB	GOSE, NP test, CPP, (2013)
Tranexamic Acid (CRASH 3)	London School of Hygiene	Y	10000	DB	Mortality in hospital, SAE, ICU days, etc (2016)
Tranexamic Acid	Khon Kaen U, Thailand Research Fund	Y	240	DB	Progressive Hemorrhage at 24hr, mortality, (2009)

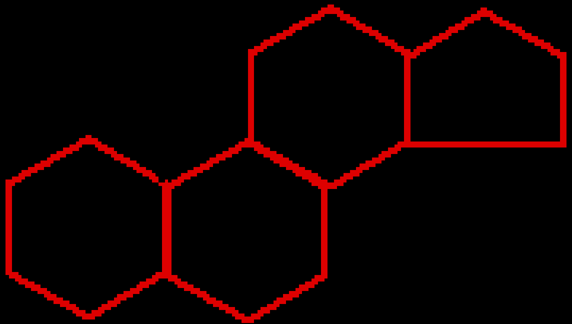
Promising Interventions



Progesterone Reduces Edema

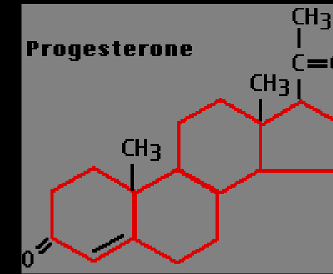
Gender, Progesterone, Brain Injury

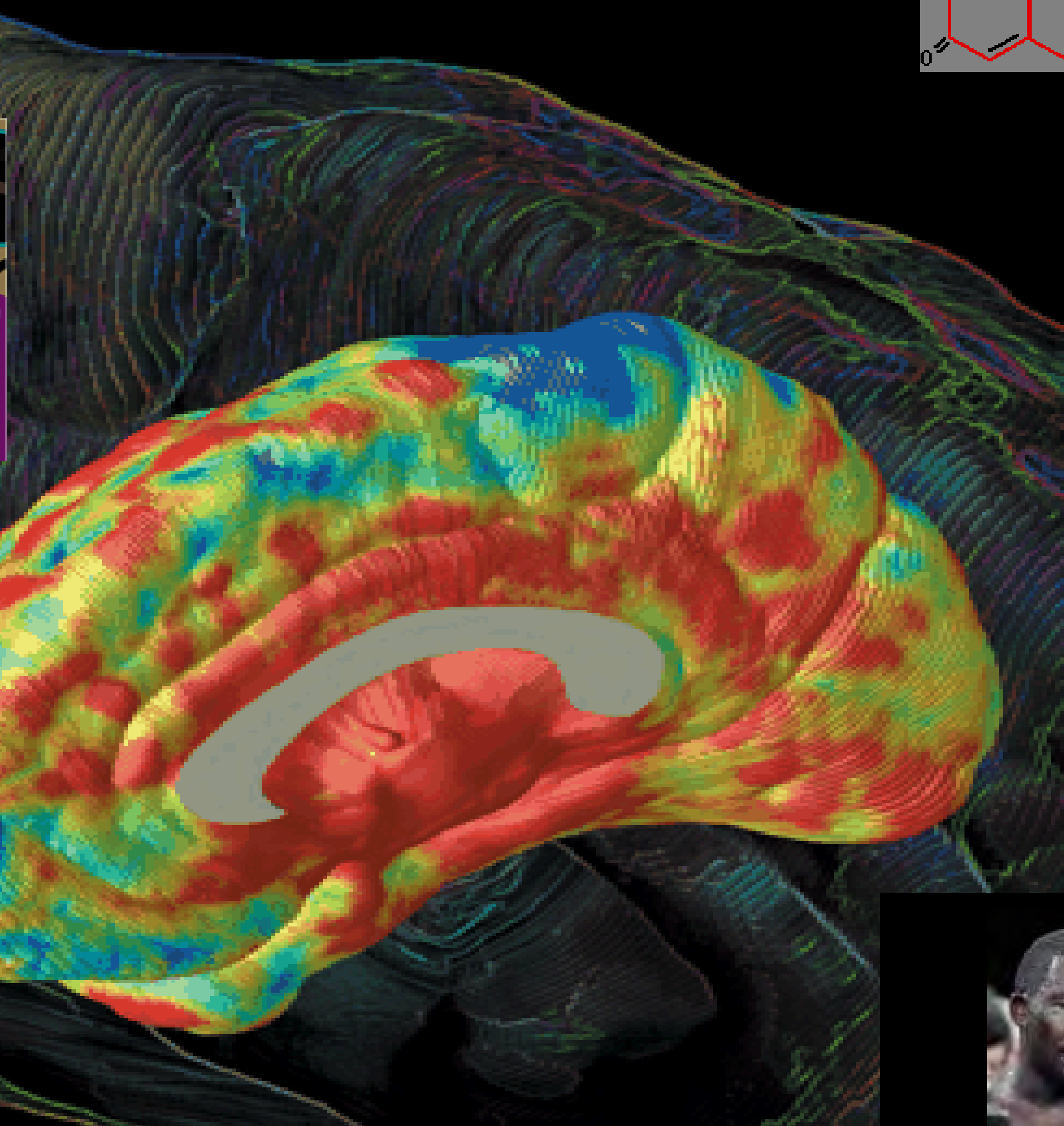


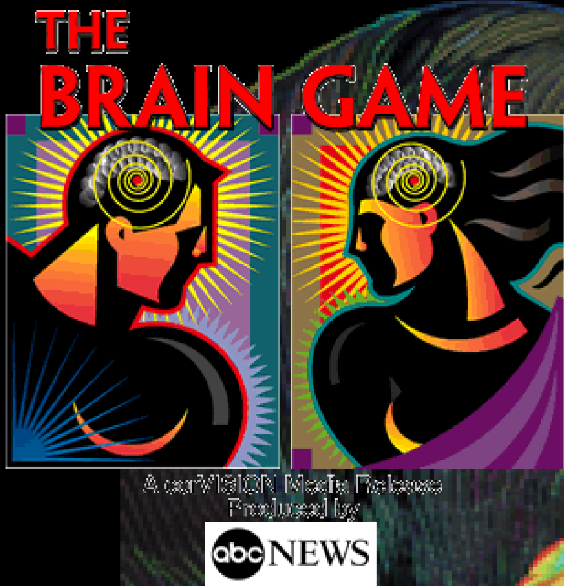


EMORY

Are There SEX Differences In The Brain?





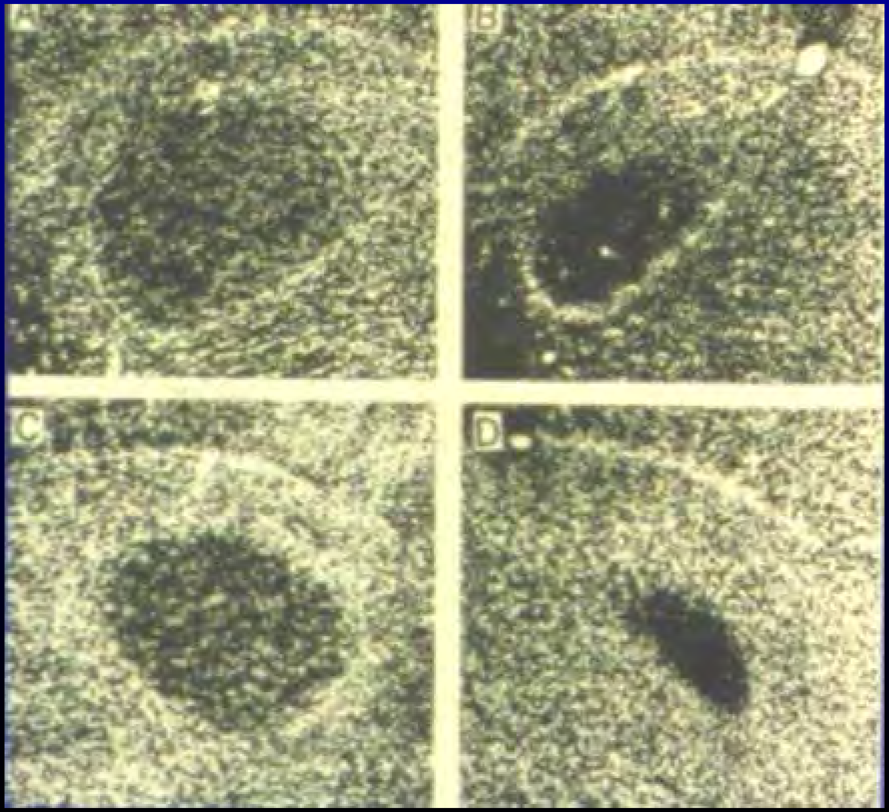


Sexual Dimorphism in a Vocal Control Area (Robust Nuc. of the Archistriatum) of the Songbird

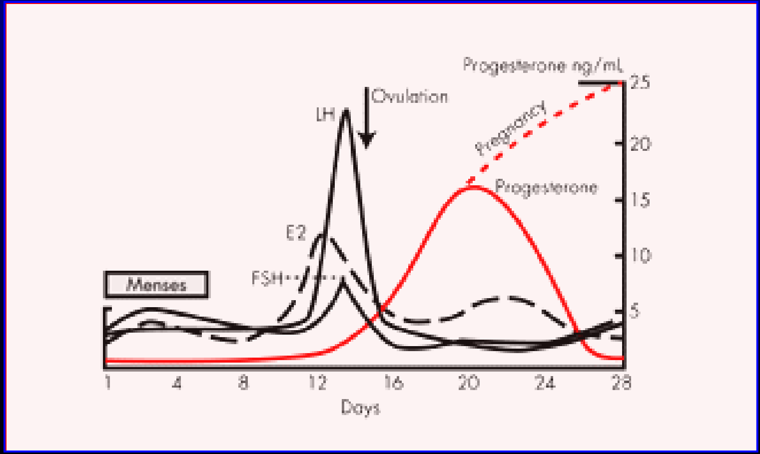
Male **Female**

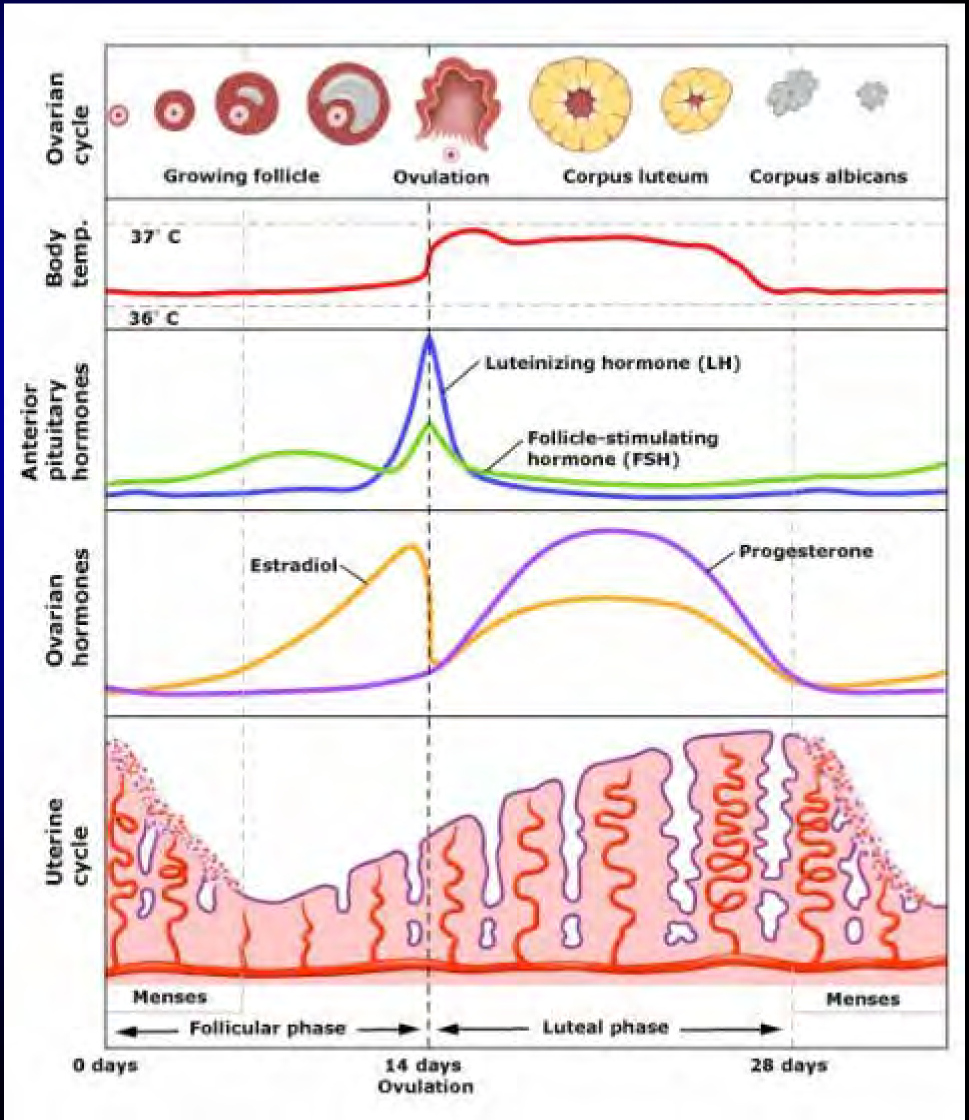
Canary

Zebra-finch

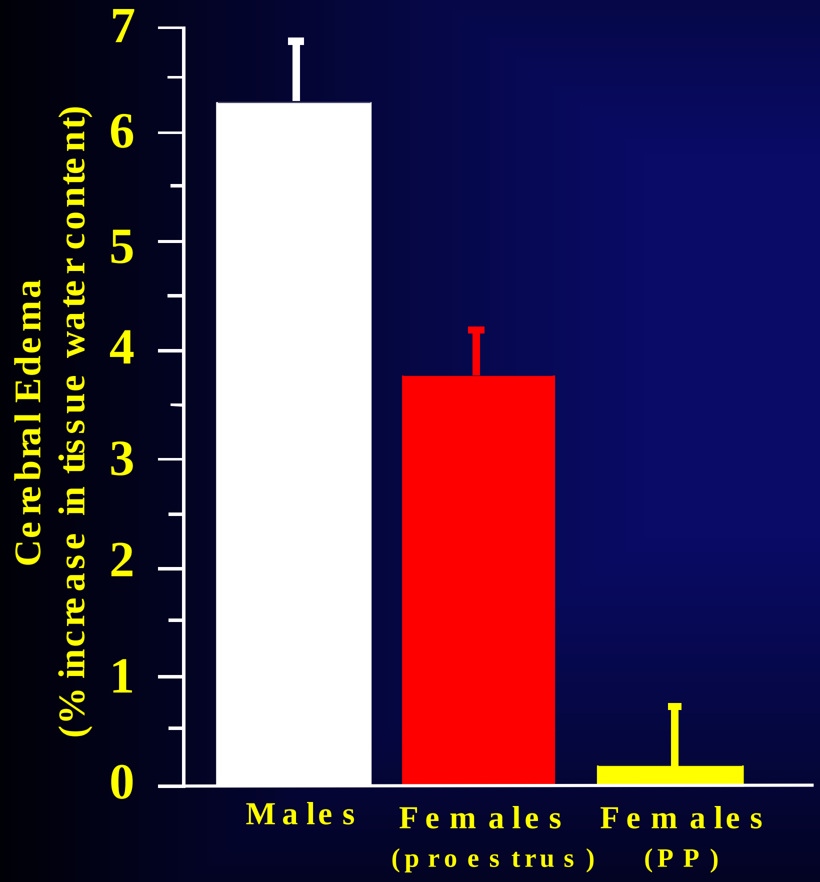


Hormonal Cycling





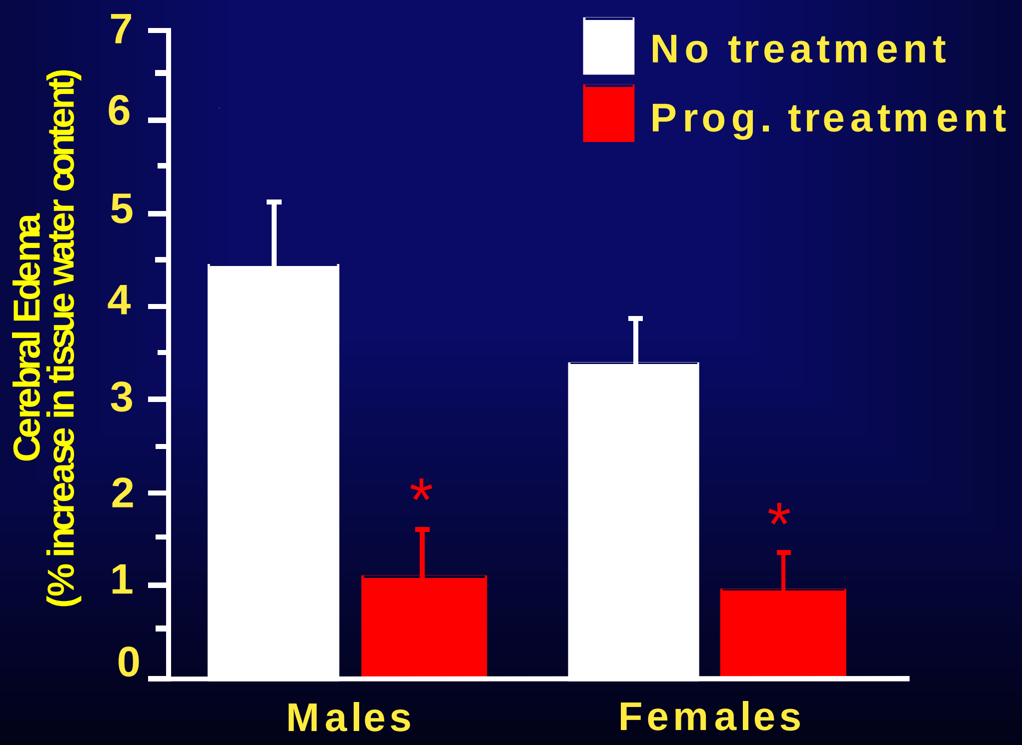
Endogenous Progesterone Reduces Edema

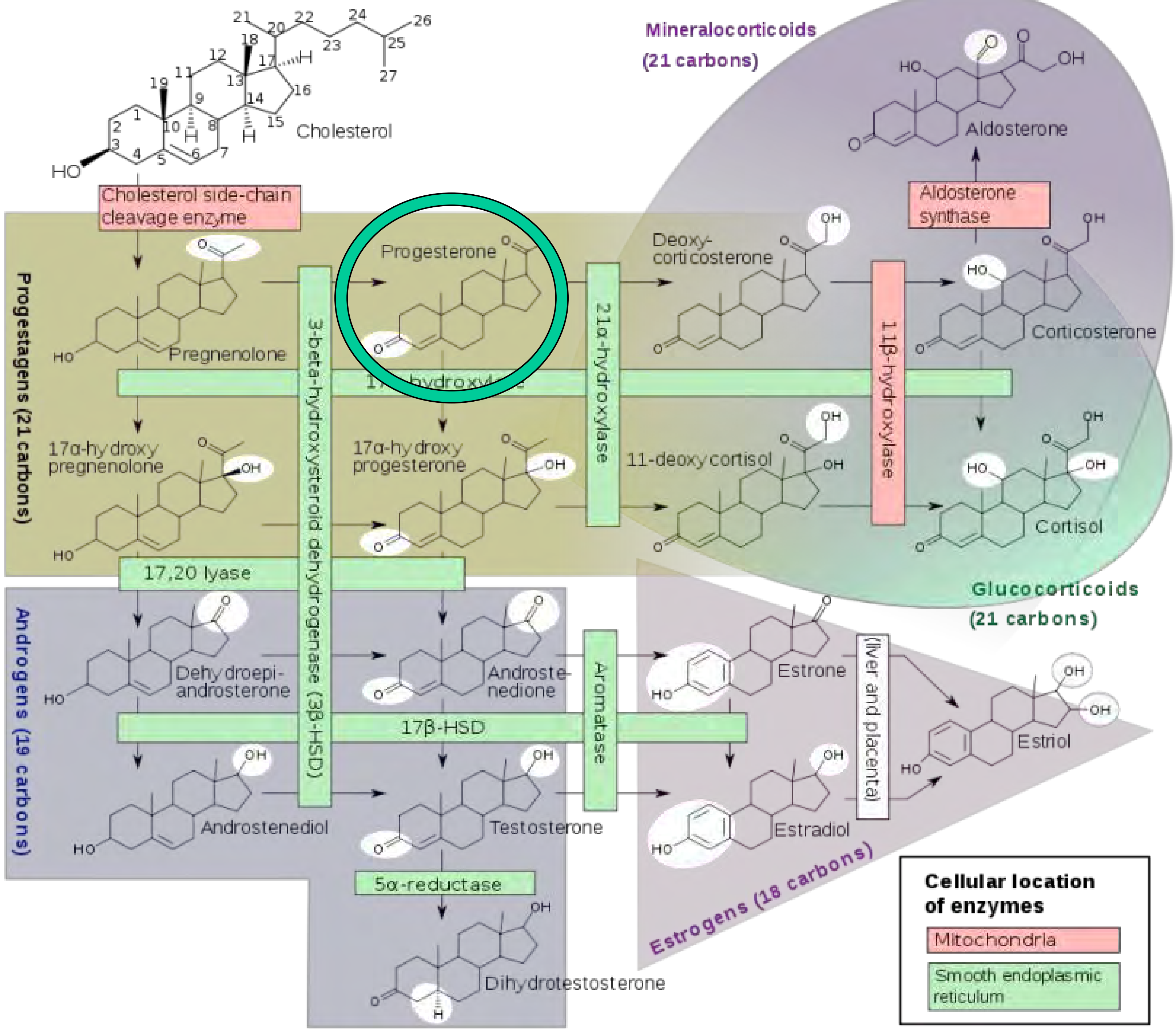


REDUCED EDEMA

Progesterone Administration

Reduces Edema in *Male* and Female Rats





Mineralocorticoids
(21 carbons)
Cholesterol
Cholesterol side-chain cleavage enzyme
Aldosterone
Aldosterone synthase
Progestagens (21 carbons)
Pregnenolone
Progesterone
Deoxy-corticosterone
Corticosterone
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
21α-hydroxylase
11β-hydroxylase
17α-hydroxylase
17α-hydroxy pregnenolone
17α-hydroxy progesterone
11-deoxycortisol
Cortisol
17,20 lyase
Glucocorticoids
(21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
Aromatase
Estrone
(liver and placenta)
Estriol
17β-HSD
Androstenediol
Testosterone
Estradiol
5α-reductase
Dihydrotestosterone
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Potential mechanisms in TBI

Remyelina

Increases Bcl2
AkT-P

Reduce Apoptosis

Mitochondrial
Recoupling

Decreases free
radicals & lipi
peroxidation

gonizes
Receptor

Vasogenic
Edema

luces Cerebral
Edema

Cytotoxic
Edema

ances
ABA

Corroborative Research

- **>180 publications showing positive results with progesterone in neurological injury**
  - 24 different laboratories
  - 4 animal species
  - 22 different animal models

Will Progesterone work in Humans?

NEUROLOGY/ORIGINAL RESEARCH

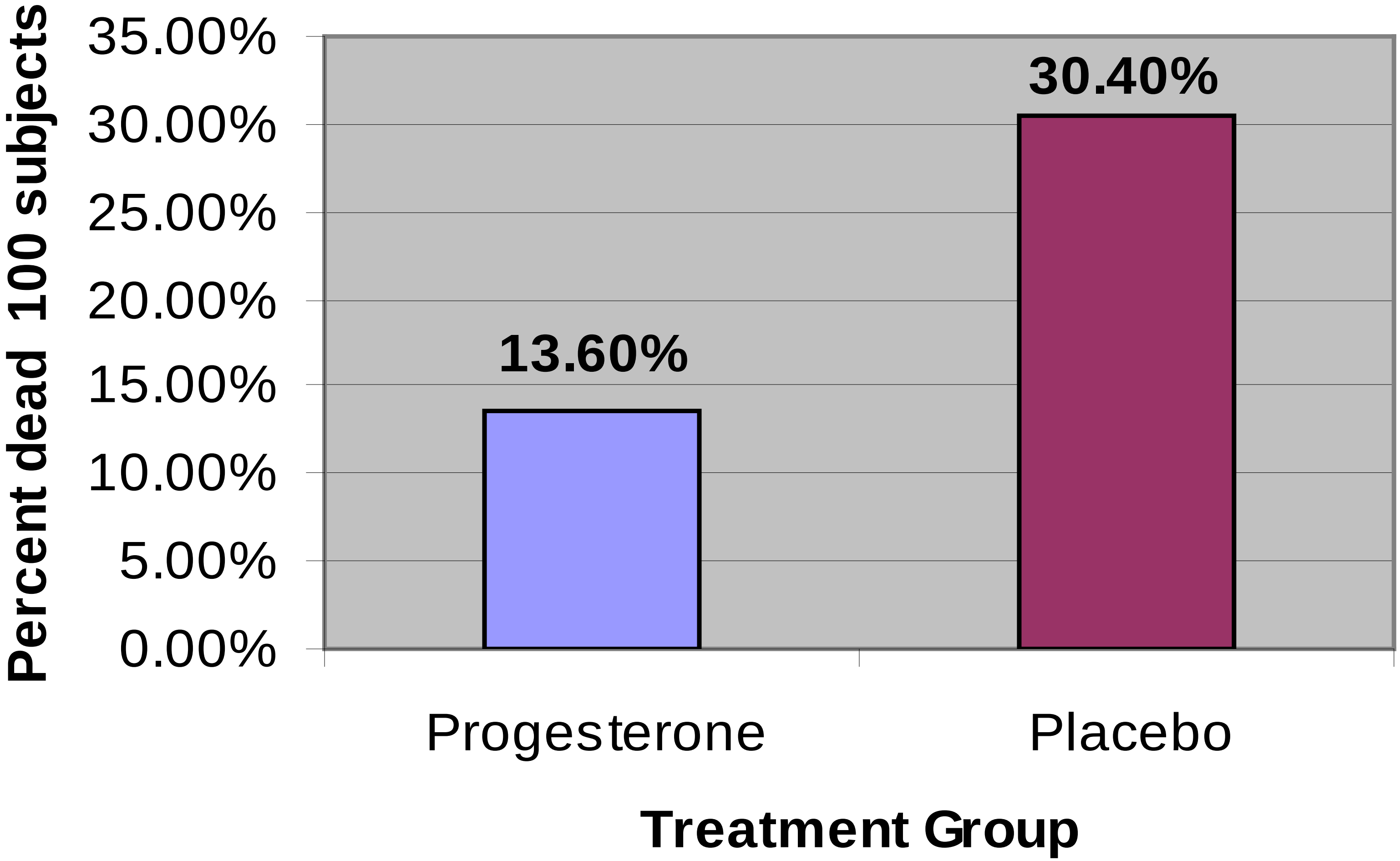
ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury

2001-2005

NINDS # 1RO1 NS39097-01A1
IRB # 433 – 2001
GCRC # 9004

Primary Outcome - Safety

30 day Mortality by Treatment



p=0.06; RR 0.43 - 95% CI (0.18-0.99)

Two Human Pilot Trials

Progesterone clinical trial designs:

	Wright et al.	***Xiao et al.***
Publication Year	2007	2008
Country	USA	China
Sites	Single-Center	Single-Center
Blinding	Double	Double
Randomization Scheme	4:1 (Tx:Pl)	1:1
Primary Goal	Safety	Efficacy
N	100	159
GCS Included	4 – 12	≤ 8
Treatment Window	<11 hours post-injury	<8 hours post-injury
Medication Administration	Loading: 0.71 mg/kg IV @ 14 mL/h x 1h Maintenance: 0.5 mg/kg IV @ 10 mL/h q12h x 3 days	1 mg/kg IM q12h x 5 days

Enrolling

PROTECT III

ProTECT™ III
Progesterone for Traumatic Brain Injury

ProTECT III PI – David W. Wright
ProTECT Project Manager – Bethany Lane
Statistician – Sharon Yeatts
Blinded Statistician – Vicki Hertzberg, Yuko Palesch
SDMC Statistical Center PI – Yuko Palesch
NETT PI – Bill Barsan, Rob Silbergleit
NETT ProTECT Site Manager – Erin Zaleski

21 Hubs Active
36/39 Sites Active

NINDS # 1U01NS062778
FDA IND # 108,144
IRB # 000-14409

ProTECT Enrollment							
Hub	Spoke	Total Enrollments (as of 2/12/13)	BioProTECT Baseline (as of 2/12/13)	BioProTECT 24 Hours (as of 2/12/13)	BioProTECT 48 Hours (as of 2/12/13)	Date of Last Enrollment	Status
Arizona	Univ of Arizona Med Ctr	30	20	20	19	1/7/13	Enrolling/BioProTECT
	Maricopa	11	9	9	7	1/4/13	Enrolling/BioProTECT
	Scottsdale	17	17	17	17	2/4/13	Enrolling/BioProTECT
	Banner	8	8	4	4	1/20/13	Enrolling/BioProTECT
	New Mexico	3	3	3	3	8/13/12	Enrolling/BioProTECT
Cincinnati	University Hospital	72	40	35	31	1/9/13	Enrolling/BioProTECT
Emory	Grady Memorial	49	15	15	14	1/17/13	Enrolling/BioProTECT
	The Med	16	11	12	12	11/28/12	Enrolling/BioProTECT
	BAMC	7	7	6	5	1/20/13	Enrolling/BioProTECT
HFHS	Henry Ford Hospital	12	7	7	7	11/3/12	Enrolling/BioProTECT
	Hurley	1	1	1	1	6/15/12	Enrolling/BioProTECT
Kentucky	University of Kentucky - Chandler	21	15	13	13	12/6/12	Enrolling/BioProTECT
Maryland	University of Maryland	3	1	1	1	3/5/12	Closed to Enrollment
	Johns Hopkins	0	0	0	0	Drug as of 10/14/11	Closed to Enrollment
Minnesota	Hennepin County Medical Center	14	8	9	9	11/8/12	Enrolling/BioProTECT
	Regions	47	31	30	29	1/23/13	Enrolling/BioProTECT
	North Memorial	6	5	5	4	2/9/13	Enrolling/BioProTECT
NYP	Columbia	2	2	2	2	8/21/12	Enrolling/BioProTECT
	Cornell	2	2	2	2	7/23/12	On Hold - pending IRB renewal
	Elmhurst						Preparing
OHSU	OHSU	28	14	13	12	12/19/12	Enrolling/BioProTECT
Stanford	Stanford	42	20	19	19	11/25/12	Enrolling/BioProTECT
	Santa Clara Valley	16	4	4	3	4/9/12	Enrolling/BioProTECT
	Reg Med Ctr, San Jose	9	9	9	9	12/28/12	Enrolling/BioProTECT
Temple	Temple University Hospital	22	10	10	10	11/24/12	Enrolling/BioProTECT
	Hershey	12	11	11	11	11/21/12	Enrolling/BioProTECT
	Jefferson	2	2	2	2	1/13/12	Enrolling/BioProTECT
	Hahnemann	7	5	6	5	8/30/12	Enrolling/BioProTECT
	Geisinger	0	0	0	0	Drug as of 7/19/11	Enrolling/BioProTECT
Texas	Memorial Hermann	55	25	24	21	1/11/13	Enrolling/BioProTECT
	Austin Brackenridge	10	5	5	5	9/28/12	Enrolling/BioProTECT
	UTSW/Parkland Health						Preparing
UCSF	San Francisco General Hospital	19	8	7	7	12/11/12	Enrolling/BioProTECT
Upenn	St Luke's	36	15	13	12	10/28/12	Enrolling/BioProTECT
	Hospital of Upenn (HUP)	15	10	9	8	1/10/13	Enrolling/BioProTECT
	Brown						Preparing
	George Washington						Preparing
VCU	VCU/MCV	24	15	15	14	10/18/12	Enrolling/BioProTECT
WSU	Detroit Receiving	14	11	10	9	2/10/13	Enrolling/BioProTECT
	Beaumont Royal Oak	1	1	1	1	4/30/12	Enrolling/BioProTECT
	Sinai Grace	3	3	3	3	11/8/12	Enrolling/BioProTECT
Wisconsin	Froedtert Memorial Hospital	64	21	18	18	10/29/12	Enrolling/BioProTECT
	Mercy St John's	0	0	0	0	Drug as of 2/21/12	Enrolling/BioProTECT
UMASS		0	0	0	0	Pending	Pending
Suny Down		0	0	0	0	Pending	Pending
OSU		0	0	0	0	Pending	Pending
Pitt		0	0	0	0	Pending	Pending
UCLA		0	0	0	0	Pending	Pending
	TOTAL Enrollment	700	391	370	349	2/10/13	17/17 Hubs Enrolling

EMORY

ProTECT^{TM} III

A Phase III, double-blind, placebo-controlled randomized clinical trial

1. Blunt traumatic brain injury
2. GCS 4-12
3. Can initiate infusion within <4 hours of injury
4. Age $\geq$18 yrs

NINDS # 1U01NS062778
FDA IND # 108,144
IRB # 000-14409

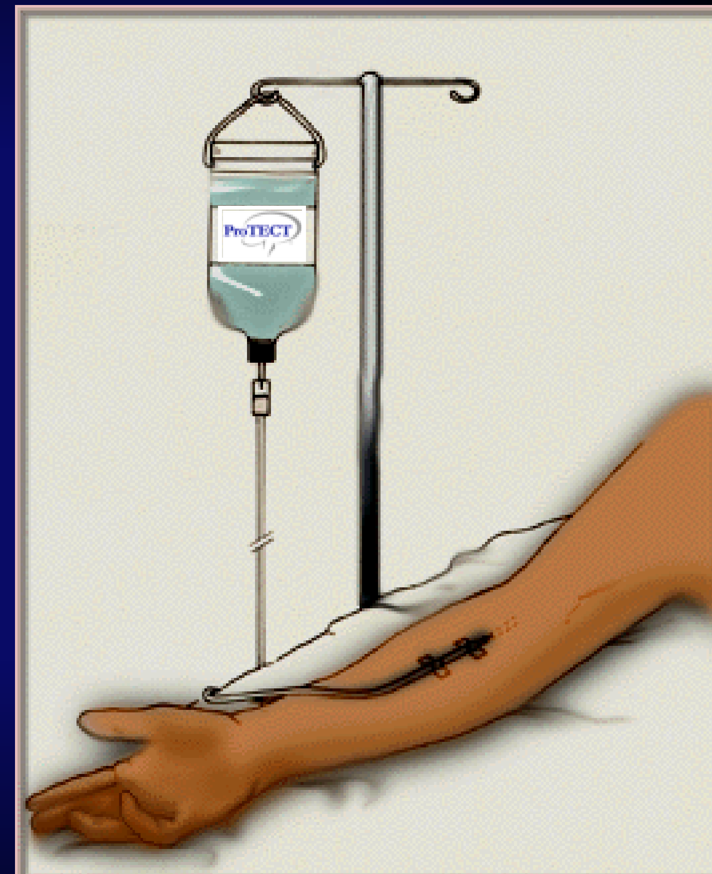
ProTECT

Investigational Drug

- Treatment: Progesterone dissolved in ethanol (~50 mg/ml) stock solution – mixed with Intralipid 20% just prior to infusion

- Placebo: Same volume of ethanol in Intralipid 20%

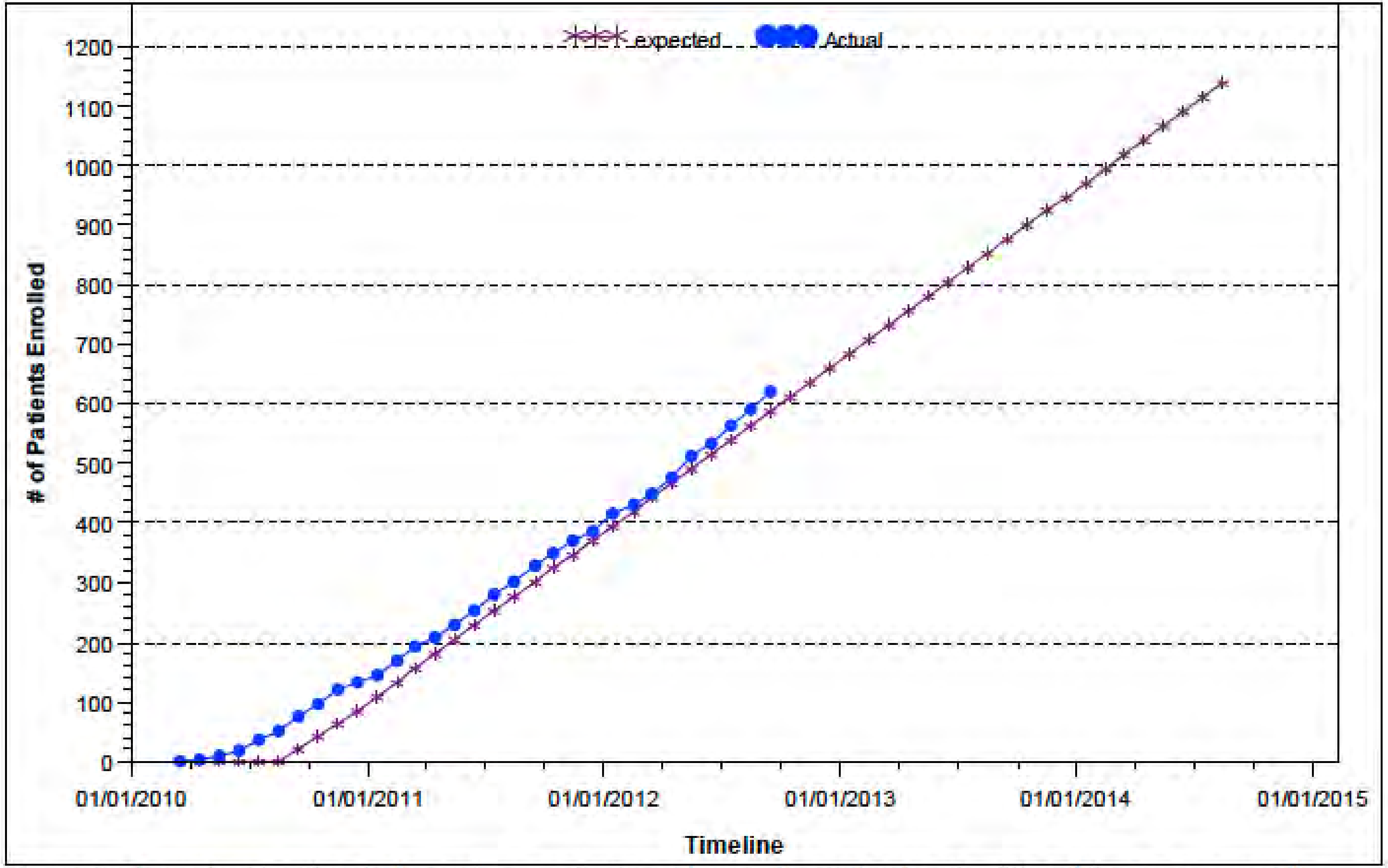
- Treatment and placebo - Not distinguishable
- Weight based formulation – 14 cc for 1 hr, then 10 cc/hr for remaining then taper)
- Infused over 4 days (72 hrs with 24 hr taper)



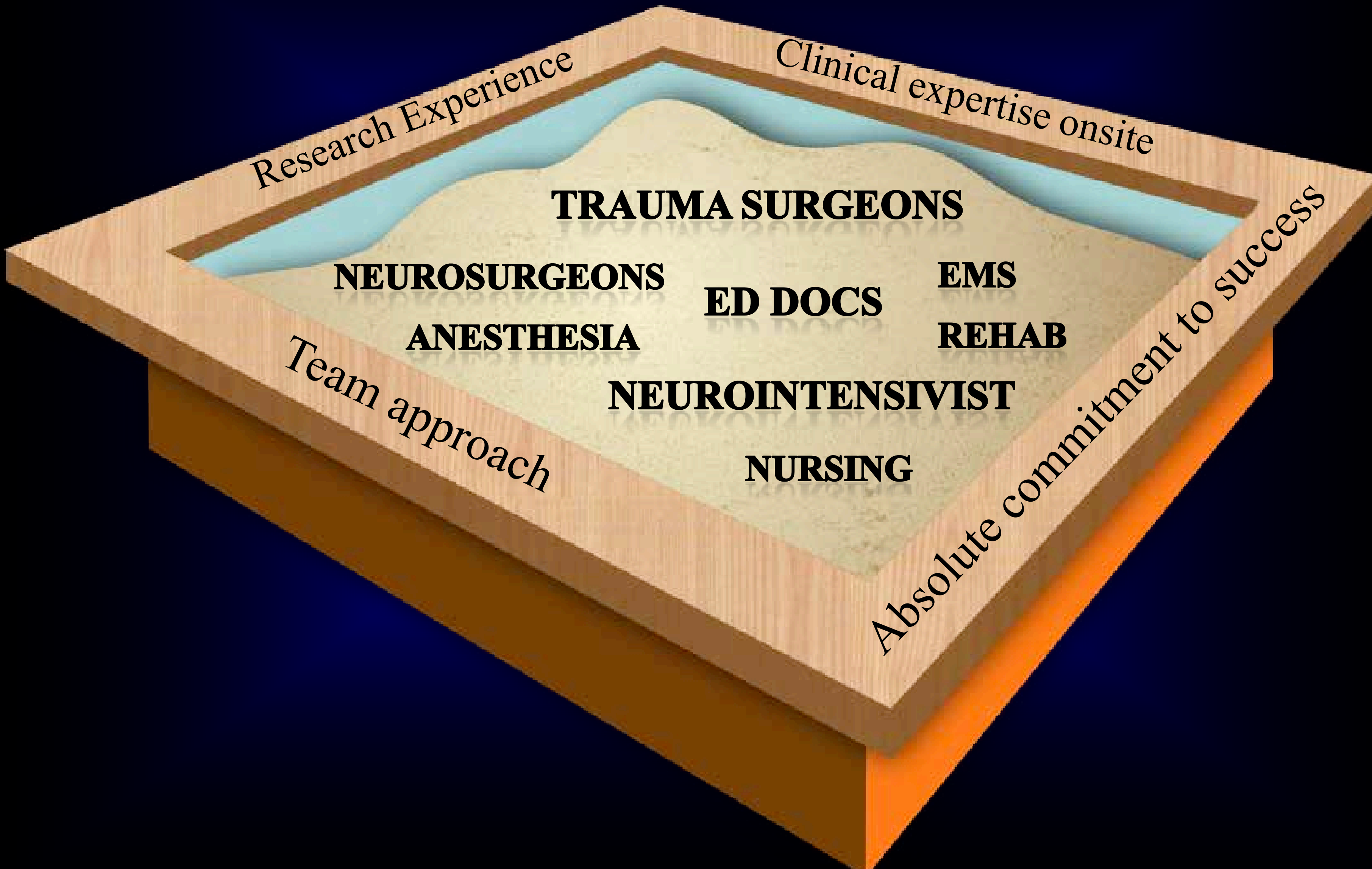
1140 subjects

6 – month Outcome

GOS-E
DRS
Mortality
NP



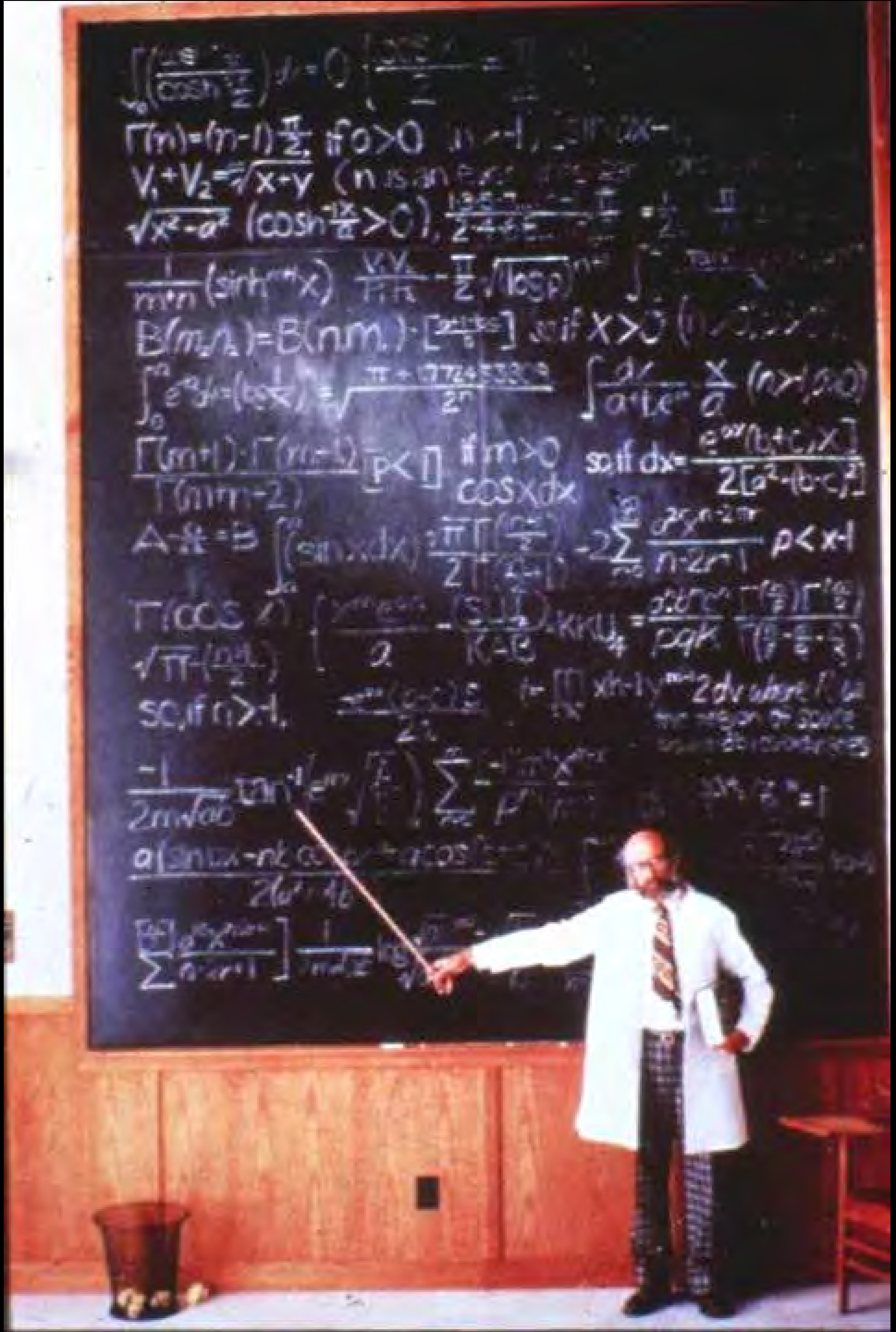
Expected randomization is based on anticipated recruitment rate of ~24 subjects per month.


Research Experience
Clinical expertise onsite
Team approach
Absolute commitment to success
TRAUMA SURGEONS
NEUROSURGEONS
EMS
ED DOCS
ANESTHESIA
REHAB
NEUROINTENSIVIST
NURSING


ProTECT™

ProTECT

Questions?



The Search for Interventions that Reversing the Cognitive and Motor Deficits the Result from Severe TBI

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Ronald G. Riechers II, MD
Suzanne S. Ruff, PhD
Cleveland Dept of Veterans Affairs Medical Center
Cleveland OH 44106

Disclosures

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Drug/Product Off-Label Use Disclosure

- None

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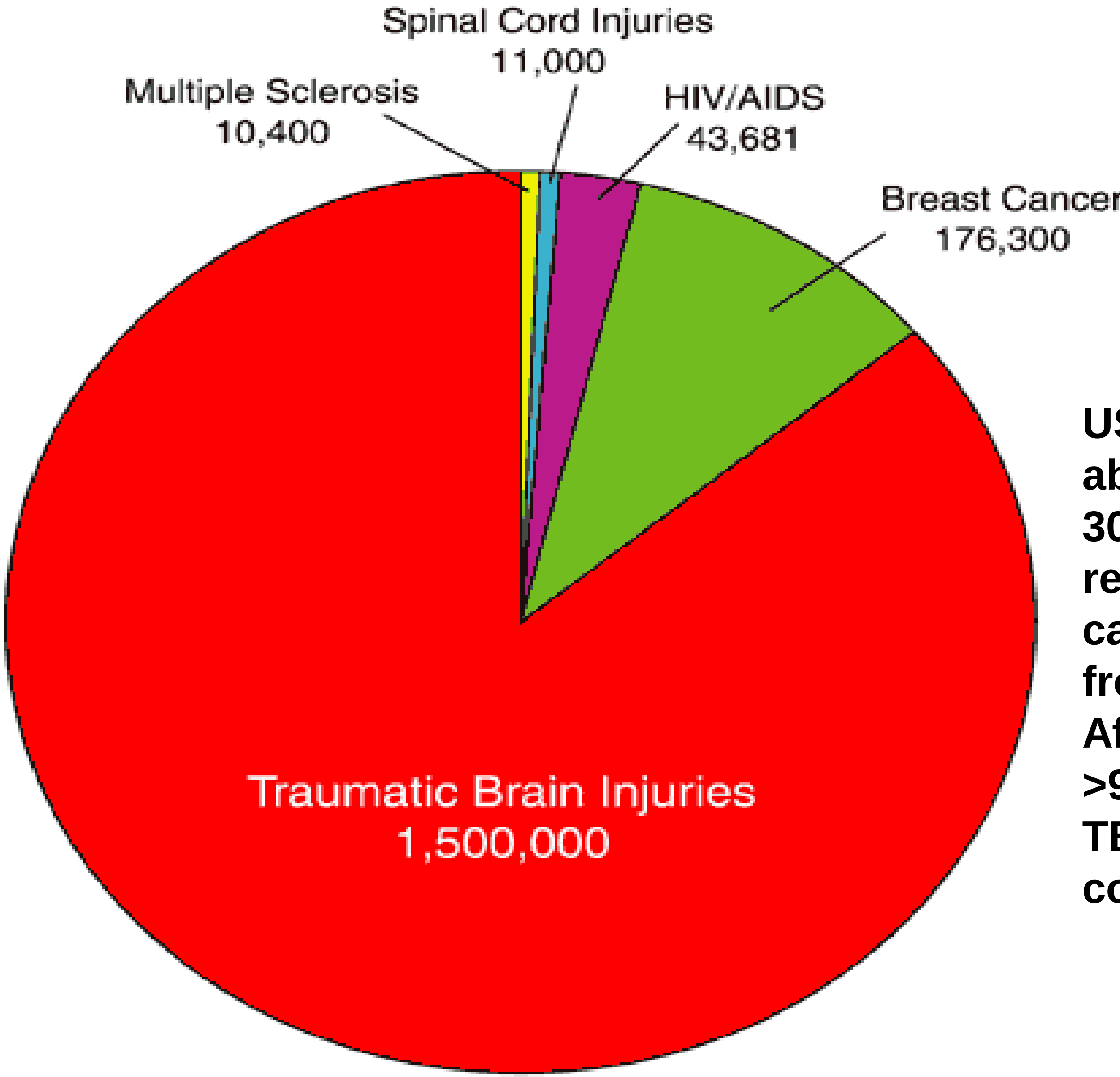
- Any opinions or conclusions presented are those of the author and do not necessarily reflect those of the Department of Veterans Affairs.



Comparison of Annual Incidence

Data compiled and arranged by the Brain Injury Association of America
based on data from the Centers for Disease Control and Prevention,
American Cancer Society and National Multiple Sclerosis Society

US Military – about 300,000 recognized cases of TBI from Iraq and Afghanistan, >90% mild TBI (aka concussion)

TBI Classification

Mild	Moderate	Severe
Normal structural imaging	Normal or abnormal structural imaging	Normal or abnormal structural imaging
LOC = 0-30 min	LOC >30 min and < 24 hours	LOC > 24 hrs
AOC = a moment up to 24 hrs	AOC >24 hours. Severity based on other criteria	
PTA = 0-1 day	PTA >1 and <7 days	PTA > 7 days
GCS=13-15	GCS=9-12	GCS=3-8

LOC - loss of consciousness, AOC - alteration of consciousness, PTA - post-traumatic amnesia, GCS – Glasgow Coma Scale ; Imaging excludes – DTI, fMRI, SPECT, PET

FIGURE 1. Average annual rates for traumatic brain injury deaths, by age group and sex — United States, 1997–2007

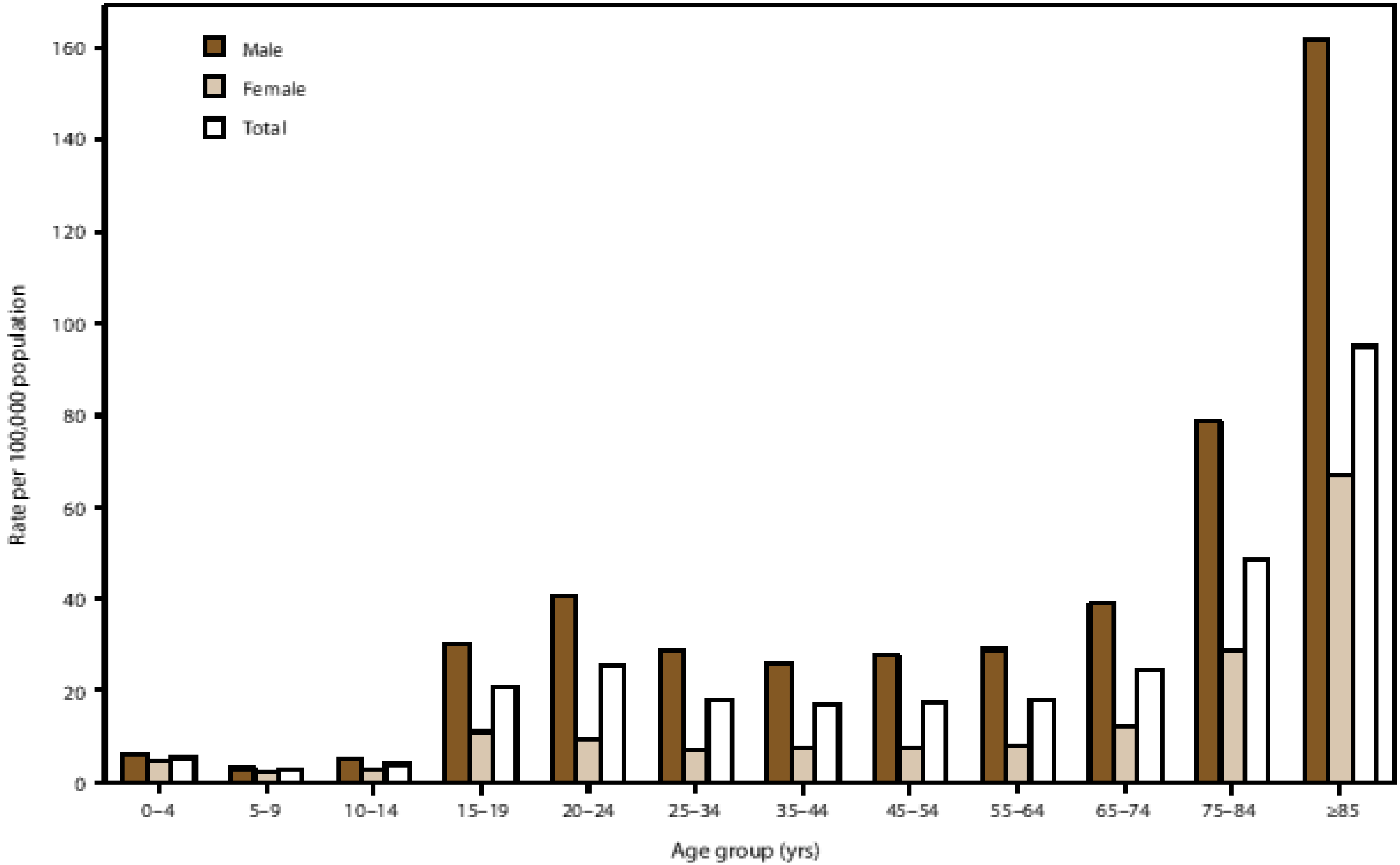
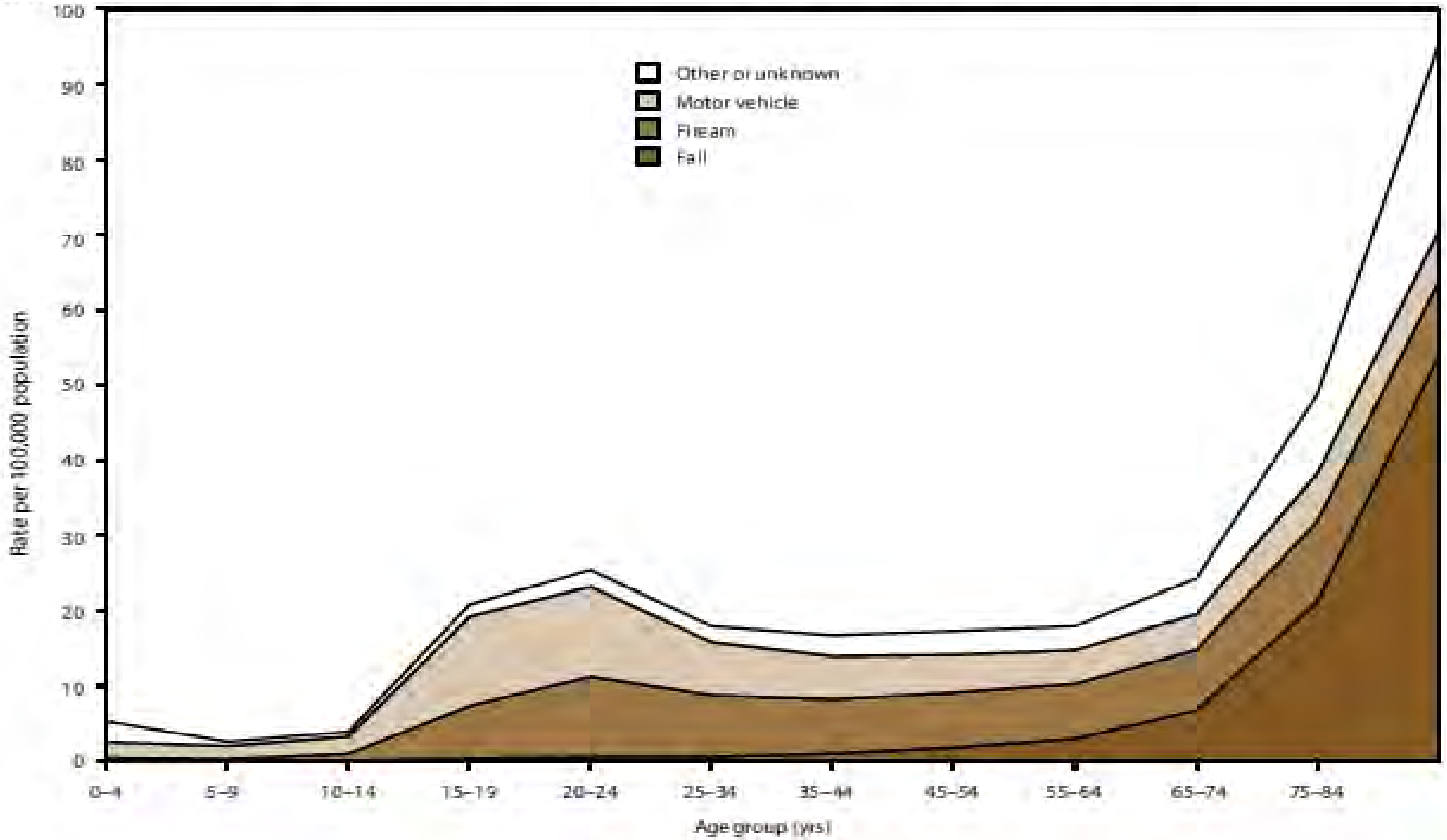
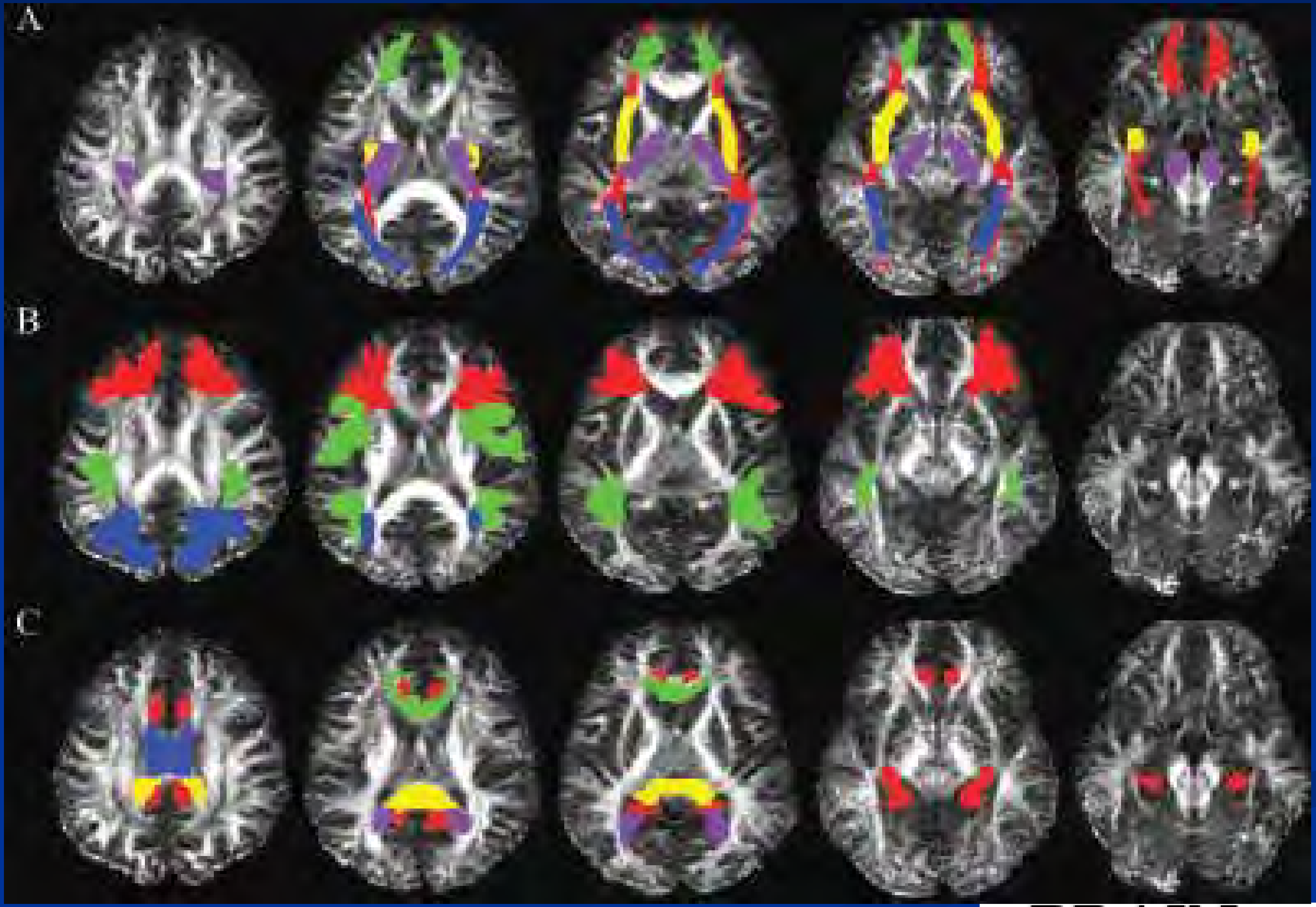


FIGURE 5. Average annual rates for traumatic brain injury deaths, by age group and external mechanism of injury — United States, 1997–2007



Example region of interest masks for a single representative subject: (A) forceps minor (green), cortico-spinal tract (purple), inferior frontal-occipital fasciculus (red), external capsule (yellow), sagittal stratum (blue); (B) anterior corona radiata (green), superior longitudinal fasciculus (red), posterior corona radiata (blue); (C) cingulum (red), corpus callosum body (blue), splenium (yellow), and genu (green) and forceps major (purple)

Mild TBI is not always benign



Kraus, M. F. et al. Brain 2007 130:2508-2519

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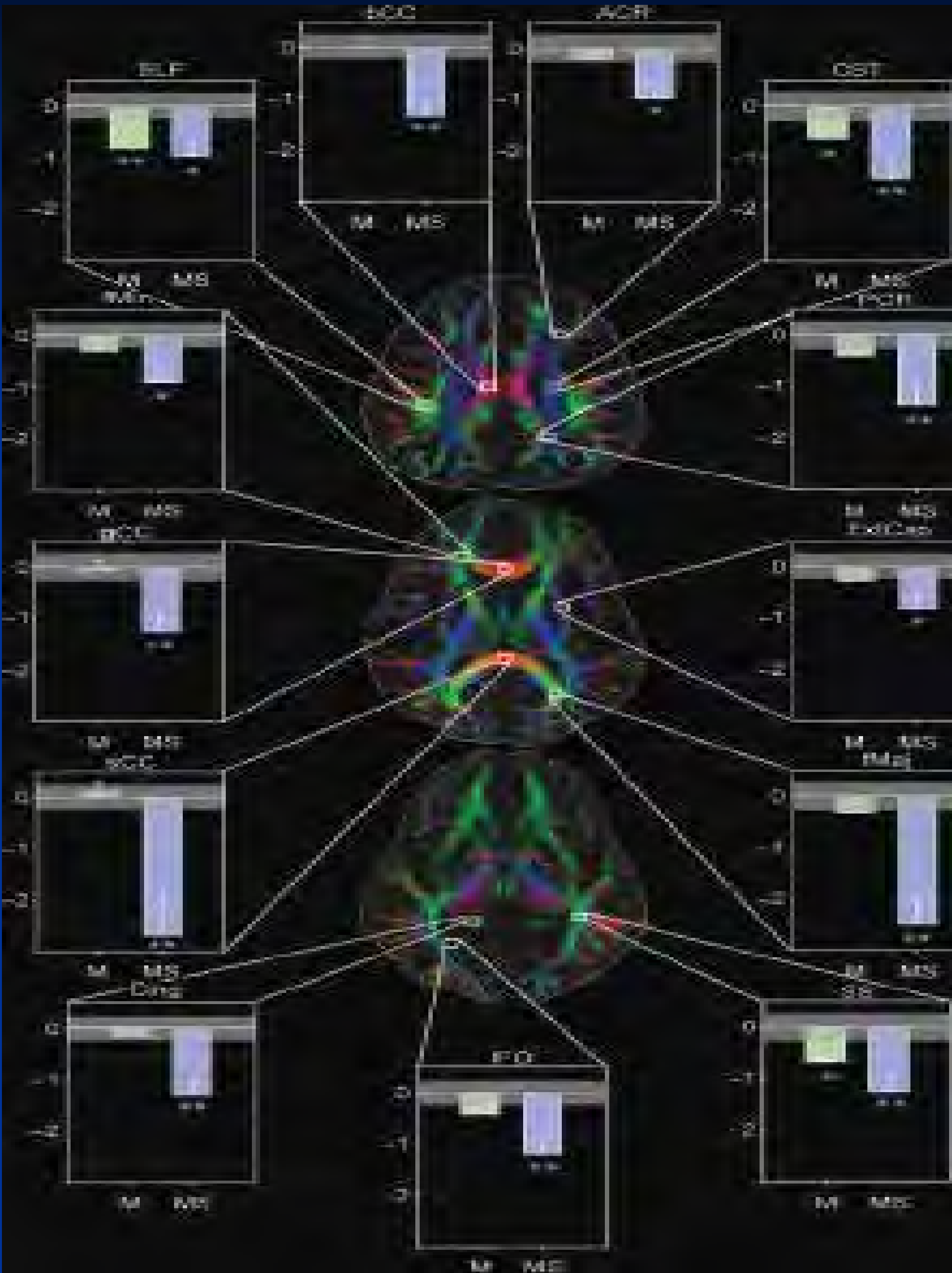
Diffusion-Tensor MRI Reveals White Matter Pathway Damage



Mild TBI (M), Moderate to Severe TBI (MS) – Note more extensive damage in MS TBI.

Preliminary results from veterans with high energy blast injury suggest that mild TBI from blast produces changes that resemble moderate non-blast TBI

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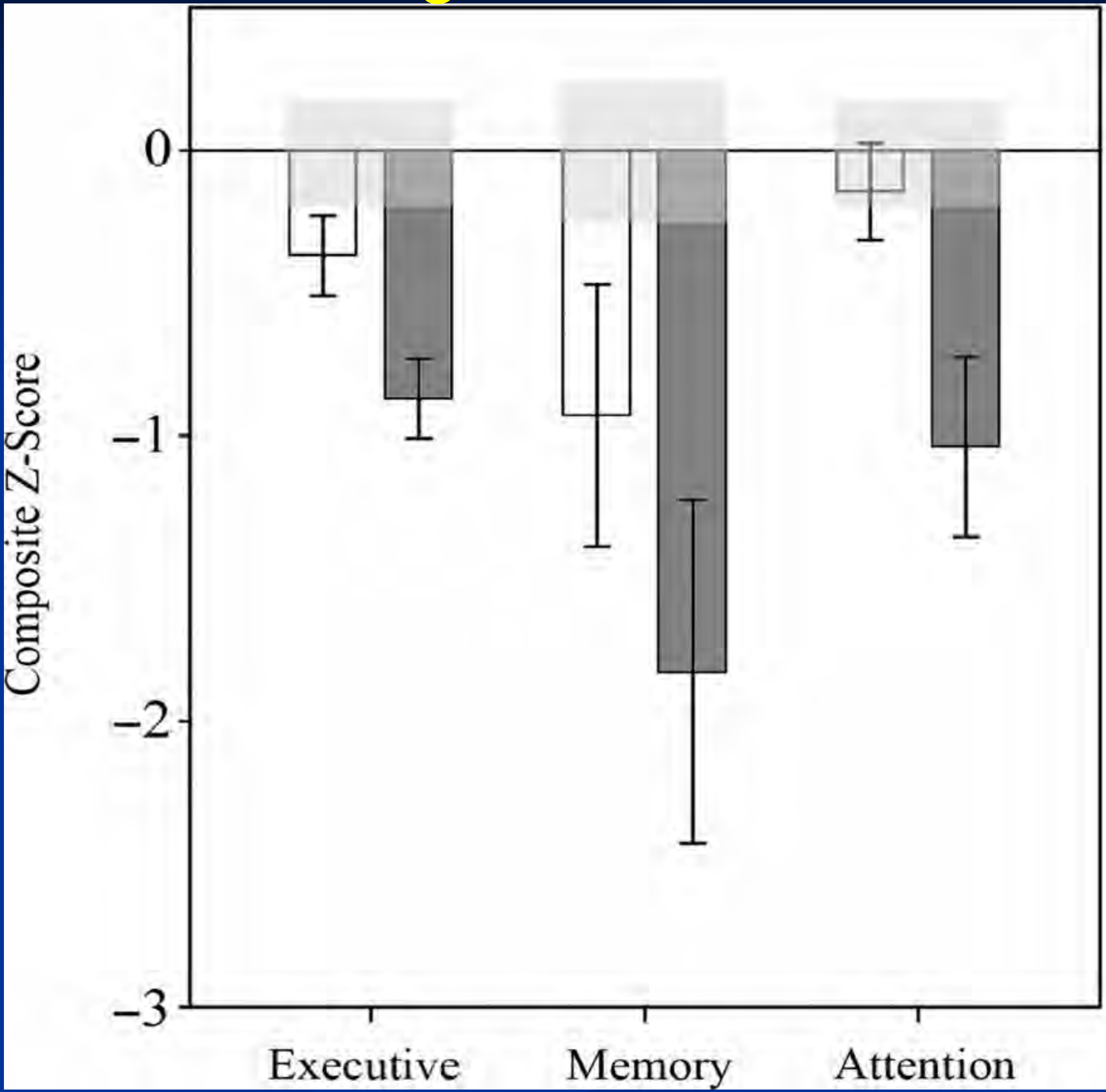
Neuropsychological Deficits Correlate with Severity of White Matter Damage

Civilian Data

Mean domain scores (normalized z-scores) for the MTBI (white) and M/STBI (dark gray)



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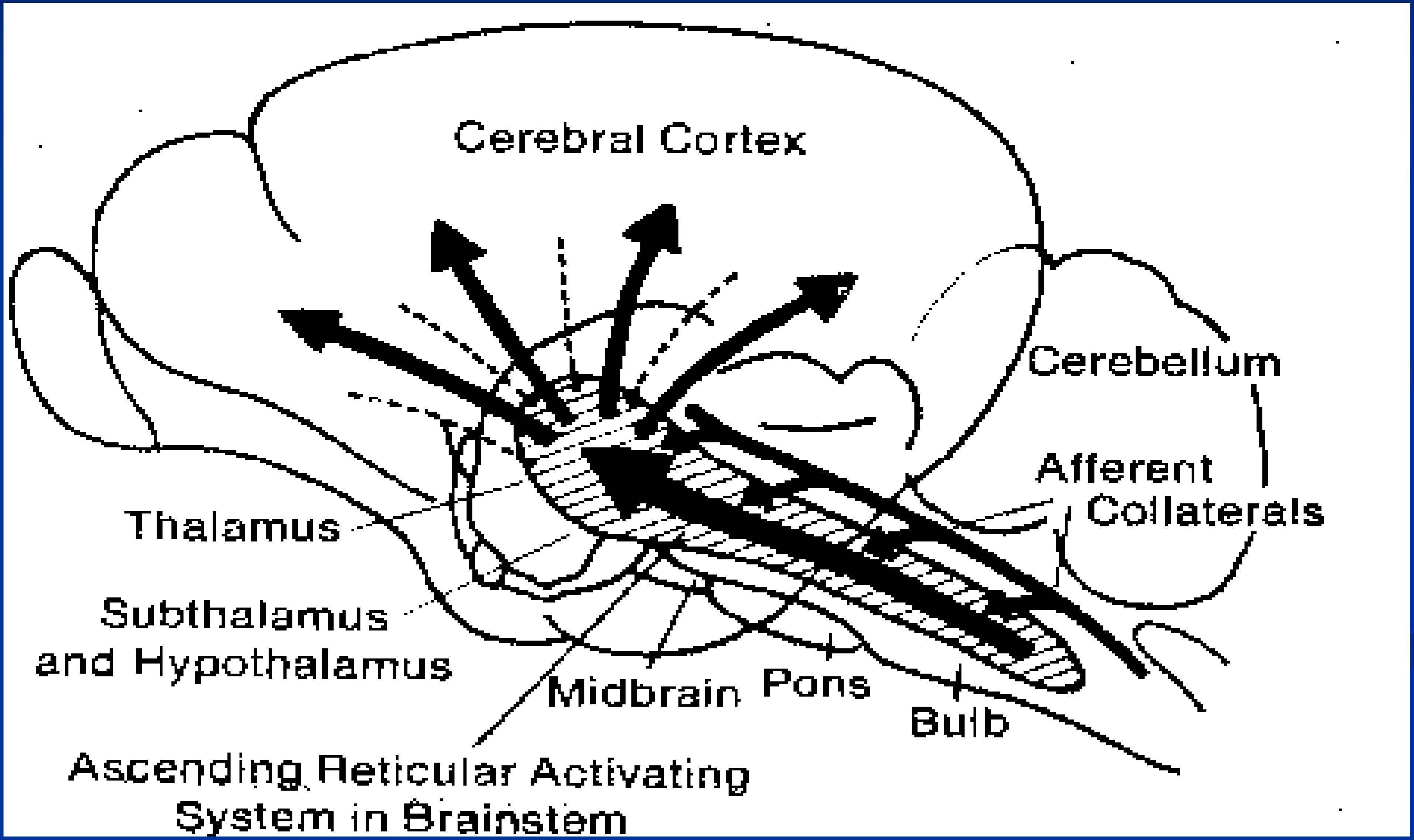
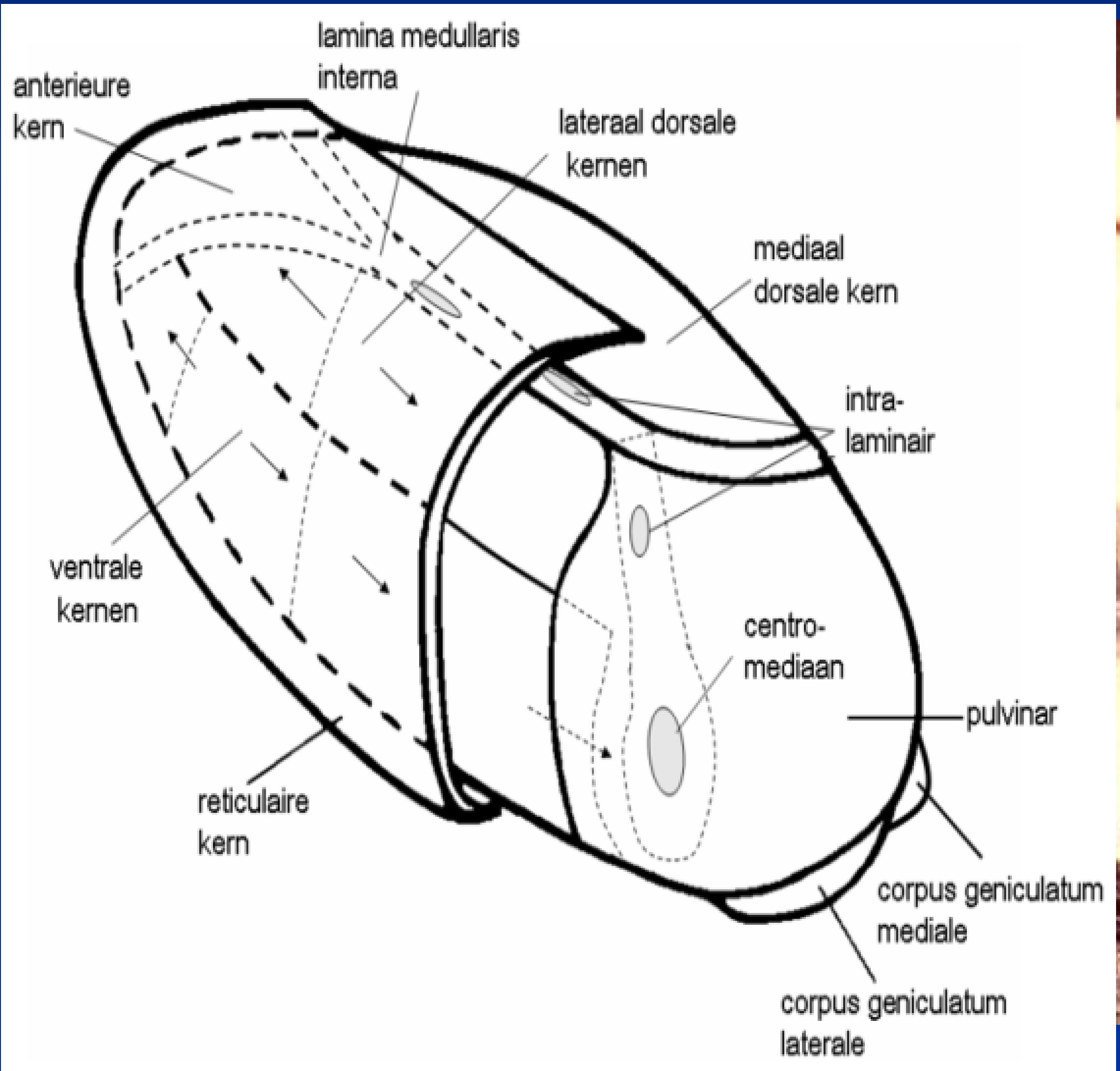
Treatments for Severe TBI

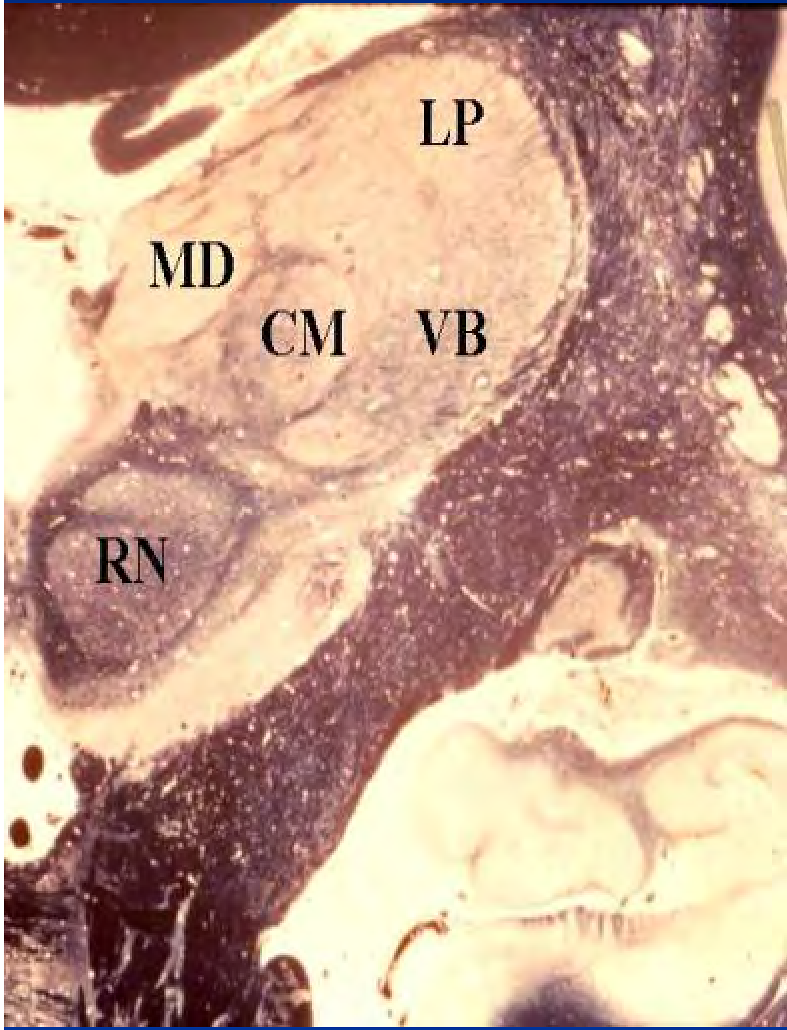
- Medication Trials – Recent trial using amantidine showed that attention improved to permit rehab. Amphetamine stimulants and not very useful
- Deep Brain Stimulation – Bilateral Stimulation of Intralaminar Nuclei for individuals with preserved language cortex and reduced cortical activation due to damage to RAS

Pontine and Midbrain RAS Activate Cortex via Intralaminar Nuclei



Intralaminar Nuclei





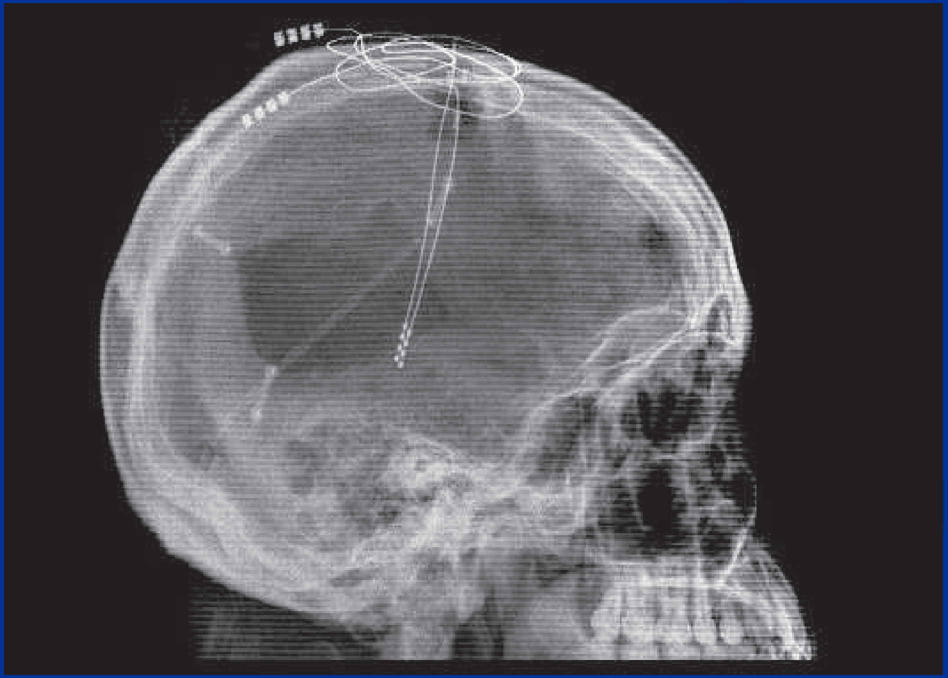
nature Vol 448 | 2 August 2007 | doi:10.1038/nature06041

LETTERS

Behavioural improvements with thalamic stimulation after severe traumatic brain injury

N. D. Schiff[1], J. T. Giacino[2,3], K. Kalmar[2], J. D. Victor[1], K. Baker[4], M. Gerber[2], B. Fritz[2], B. Eisenberg[2], J. O'Connor[2], E. J. Kobylarz[1], S. Farris[4], A. Machado[4], C. McCagg[2], F. Plum[1], J. J. Fins[5] & A. R. Rezai[4]

In the latest case study, neuroscientists describe how they implanted electrodes in the brain of a 38-year-old man who had been in a minimally conscious state for more than six years following a serious assault. By electrically stimulating a brain region called the central thalamus, they were able to help him name objects on request, make precise hand gestures, and chew food without the aid of a feeding tube



Citicoline – Unrealized Promise

- Intermediate in the generation of phosphatidylcholine
- Brain uses choline to synthesize acetylcholine
- Animal studies and preliminary clinical pilot studies citocoline reduced cerebral injury from TBI & ischemia
- However, in randomized clinical trials, Citicoline was ineffective in TBI (Zafonte et al. 2012) or stroke (Dávalos et al. Lancet 2012)

Why Did Citicoline Fail?

1. Animals may have more resilient brains – perhaps rodents are not the best model
2. Citicoline might improve only some aspects of functional clinical recovery
3. Motor and cognitive rehabilitation are critical for optimal recovery could not control
4. One of the major mechanisms of clinical brain damage in TBI is diffuse axonal injury – the injuries in the patients have been far more extensive then just DAI

Thank You

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